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Network Pharmacology-Based Study on the Efficacy and Mechanism of *Lonicera japonica* Thunberg

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Abstract: Network pharmacology is an emerging method for investigating the potential effects and mechanisms of natural products through system-level analyses of gene sets in herbs. *Lonicera japonica* Thunberg (LJ) is known to have anti-inflammatory, anti-bacterial, anti-oxidant, anti-tumor and neuroprotective effects. In the present study, network pharmacological analysis was performed to assess the potential efficacy and mechanisms of LJ. First of all, constituents of LJ were gathered from public databases: the Oriental Advanced Searching Integrated System (OASIS) database, PubChem and the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database. Then, a network was constructed using Cytoscape3.8.2, which visualizes biomedical interactions, and a functional enrichment analysis was conducted to uncover the pathways most relevant to LJ through Enrichr based on the Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway 2021. Further, we performed a study of the literature to determine whether the results of our study were consistent with those of previous studies. The results showed that 'Advanced glycation end products-Receptor for advanced glycation end products (AGE-RAGE) signaling pathway in diabetic complications' was the pathway most relevant to LJ, especially through 'Mitogen-activated protein kinase (MAPK) signaling pathway', 'Phosphatidylinositol 3 kinase-Protein kinase B (PI3K-AKT) signaling pathway' and 'Janus kinase-Signal transducers and activators of transcription (JAK-STAT) signaling pathway'. Based on the literature study, LJ showed relevance to MAPK, PI3K-AKT and JAK-STAT and was associated with therapeutic effects on diabetes and diabetic complications. This study shows that network pharmacology can be a suitable approach for analyzing LJ and suggests the potential efficacy and mechanisms of LJ.

Keywords: *Lonicera japonica* Thunberg; network pharmacology; potential efficacy; age-rage signaling pathway; diabetic complications

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1. Introduction

Over the past decades, drug development has involved considerable stages, including compound screening, mechanistic studies and cell and animal experiments, followed by human clinical studies. Conventional experimental methods, such as in vitro or in vivo experiments, have mainly been utilized to investigate the molecular mechanisms and therapeutic effects of herbs [1]. Although many reports have attempted to discover the mechanisms and efficacies of natural products for medicinal use, understanding the entire systemic functions of herbs is still challenging because of their numerous constituents and targets. Network pharmacology is known to be an emerging approach for investigating system-level mechanisms of drugs [2]. Recently, network pharmacology-based studies have been conducted to examine the integrated efficacies of herbs and to improve efficiency in pharmaceutical development [3–5]. They enable multiple components to be combined and system-level analyses to be performed with huge gene sets [6–8]. Based on data for chemical compounds and target genes, network-analytic methods have been used to predict potential pathways of herbs in several studies. The bioactive ingredients of

the Huangqin–Baishao herb pair were identified and its anticancer mechanisms were revealed through a pharmacology approach [9]. The anti-proliferative effects of *polygonum cuspidatum* on gynecological cancer cells were validated using a series of functional assays, which demonstrates that the network pharmacology approach is reliable and powerful enough to guide mechanistic studies of herbs [10]. Five core herbs (*Yanhusuo, Gouteng, Huangbai, Lianqiao* and *Gancao*) were identified to have great potential against antineoplastic drug-induced cardiotoxicity based on network pharmacology and data mining [11].

Lonicera japonica Thunberg (LJ) has been used for therapeutic purposes, such as exopathogenic wind-heat, epidemic febrile diseases, sores, carbuncles, furuncles and some infectious diseases, in traditional medicine [12]. LJ has been known to exert anti-inflammatory, anti-bacterial, anti-oxidant, anti-tumor and neuroprotective effects [13–17]. There is a report that LJ includes various chemical constituents, such as logainin, sweroside, rutin, luteoloside, lonicerin, centauroside and (E)-aldosecologanin [18]. Despite all the investigations that have been undertaken to identify the molecular mechanisms of LJ, the integrated therapeutic effects of LJ based on its components have not yet been fully clarified. The aim of the present study is to assess the potential efficacy and mechanisms of LJ through network pharmacological analysis. To begin with, the components of LJ were collected through open scientific databases. After that, a network for LJ was constructed to investigate correlations between components and features of LJ. Lastly, a functional enrichment analysis was performed to examine the specific mechanisms and potential efficacy of LJ. A literature study was also undertaken to confirm whether the results were reliable.

2. Materials and Methods

2.1. Compound and Target Gene Collection

In order to construct an LJ network, constituents of LJ were collected from public databases. Compounds of LJ were collected through the Oriental Advanced Searching Integrated System (OASIS) database (https://oasis.kiom.re.kr/, accessed on 15 June 2022). OASIS is a Korean medical database which contains traditional medicine studies and herbal information. It provides biochemical information for 478 herbs, including LJ. Based on the OASIS database, 26 active compounds of LJ, including loganin, sweroside and quercetin, were identified along with their molecular formulae and PubChem Compound identification numbers (CIDs) (Table 1). Targets, which are chemical genes, associated with each compound were collected through the PubChem database (https://pubchem.ncbi.nlm.nih.gov/, accessed on 15 June 2022) [19]. The PubChem database contains various items of chemical information, such as names, molecular formulae, structures and other identifiers. A total of 1662 target genes were identified as co-occurring with the compounds (Table S1). Out of the 1662 targets, after removing duplicates, 359 targets were sorted via the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database (http://www.string-db.org/, accessed on 15 June 2022) with a score $\geq$0.7, which represents a high confidence rate [20]. In total, 359 targets were selected as potential targets of LJ and used to construct the LJ network.

Table 1. Active compounds of *Lonicera japonica* Thunberg (LJ). The 26 compounds and their PubChem compound identification numbers (CIDs) based on the Oriental Advanced Searching Integrated System (OASIS) database.

Compound Name	Molecule Formula	PubChem CID
Centauroside	$C_{34}H_{46}O_{19}$	102183195
Demethylsecologanol	$C_{16}H_{24}O_{10}$	11617742
5-O-caffeoylquinic acid	$C_{16}H_{18}O_9$	12310830
Ketologanin	$C_{16}H_{22}O_{10}$	12311348
1,4-di-O-caffeoylquinic acid	$C_{25}H_{24}O_{12}$	12358846
Sweroside	$C_{16}H_{22}O_9$	161036
Secologanin acid	$C_{17}H_{24}O_{10}$	161276
Secoxyloganin	$C_{17}H_{24}O_{11}$	162868

Table 1. *Cont.*

Compound Name	Molecule Formula	PubChem CID
Chlorogenic acid	$C_{16}H_{18}O_9$	1794427
(E)-aldosecologanin	$C_{34}H_{46}O_{19}$	45783101
Quercetin	$C_{15}H_{10}O_7$	5280343
Coniferin	$C_{16}H_{22}O_8$	5280372
Luteolin	$C_{15}H_{10}O_6$	5280445
Neochlorogenic acid	$C_{16}H_{18}O_9$	5280633
Luteoloside	$C_{21}H_{20}O_{11}$	5280637
Isoquercitrin	$C_{21}H_{20}O_{12}$	5280804
Rutin	$C_{27}H_{30}O_{16}$	5280805
Hyperoside	$C_{21}H_{20}O_{12}$	5281643
3,4-O-dicaffeoylquinic acid	$C_{25}H_{24}O_{12}$	5281780
Rhoifolin	$C_{27}H_{30}O_{14}$	5282150
Lonicerin	$C_{27}H_{30}O_{15}$	5282152
4,5-O-dicaffeoylquinic acid	$C_{25}H_{24}O_{12}$	6474309
Isochlorogenic acid A	$C_{25}H_{24}O_{12}$	6474310
Caffeic acid	$C_9H_8O_4$	689043
Loganin	$C_{17}H_{26}O_{10}$	87691
Loganic acid	$C_{16}H_{24}O_{10}$	89640

2.2. Network Construction

The network for LJ was constructed to investigate the integrated therapeutic effects of LJ by analyzing connections in the network. The 365 targets, including *AKT1*, *INS*, *IL6*, *STAT3* and *TP53*, were used to create the network using Cytoscape3.8.2 (http://www.cytoscape.org/, accessed on 15 June 2022) [21]. Cytoscape is an open-source software tool for the visual exploration of biomedical networks which include protein, gene and other types of interactions. As a result, a network with 359 nodes and 2891 edges was created. The nodes and the edges represent targets of LJ and connections between the nodes, respectively.

2.3. Functional Enrichment Analysis

A functional enrichment analysis [22] was attempted to analyze the LJ network, using Enrichr (https://maayanlab.cloud/Enrichr/, accessed on 15 June 2022) [23], based on the Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway 2021 (www.kegg.jp/pathway, accessed on 15 June 2022) [24]. Enrichment analysis is a method used to analyze massive number of genes and disclose relevant pathways. Enrichr is a database that consists of diverse gene set libraries and a tool with which to perform a functional enrichment analysis. KEGG Pathway 2021 is a collection of manually drawn reference pathway maps and organism-specific pathway maps that are computationally generated by genes and proteins in humans. The enrichment analysis was conducted to analyze the LJ network and predict the potential efficacy and mechanisms of LJ. The *p*-values and combined scores of the pathways were presented. The *p*-values were computed using standard statistical methods, such as Fisher's exact test or the hypergeometric test. The combined score is a combination of the *p*-value and *z*-score calculated by multiplying the two scores as follows: $c = ln(p) * z$. The *z*-scores were computed using a modification of Fisher's exact test for deviation from an expected rank.

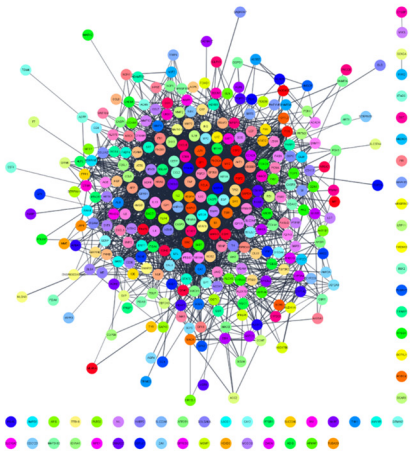
3. Results

3.1. Network Analysis of LJ

The LJ network was analyzed according to the degrees of nodes and edges to recognize the main targets and potential functions of LJ. The LJ network consisted of 359 nodes, which represent target genes, and 2891 edges, which represent their connections (Figure 1A). The top 10 genes with the highest edge degrees were *AKT1*, *INS*, *IL6*, *STAT3*, *TP53*, *JUN*, *VEGFA*, *MAPK8*, *TNF* and *MAPK1* (Figure 1B). AKT1, the protein name for which is *Proline-rich*

AKT1 substrate 1, had 99 edges, which indicates that AKT1 is associated with 99 other targets in the network. Based on the Gene Ontology (GO) Biological Process category database [25], the functions of the top 10 genes were collected. 'Negative regulation of cell size' and 'negative regulation of protein kinase activity' were regarded as known functions of AKT1. INS, which is *Insulin*, had 95 edges in the network and was known to have 'activation of protein kinase B activity' and 'acute-phase response' functions based on GO Biological Process. In the same way, the protein names for and functions of other targets—*IL6*, *STAT3*, *TP53*, *JUN*, *VEGFA*, *MAPK8*, *TNF* and *MAK1*—were derived.

A.



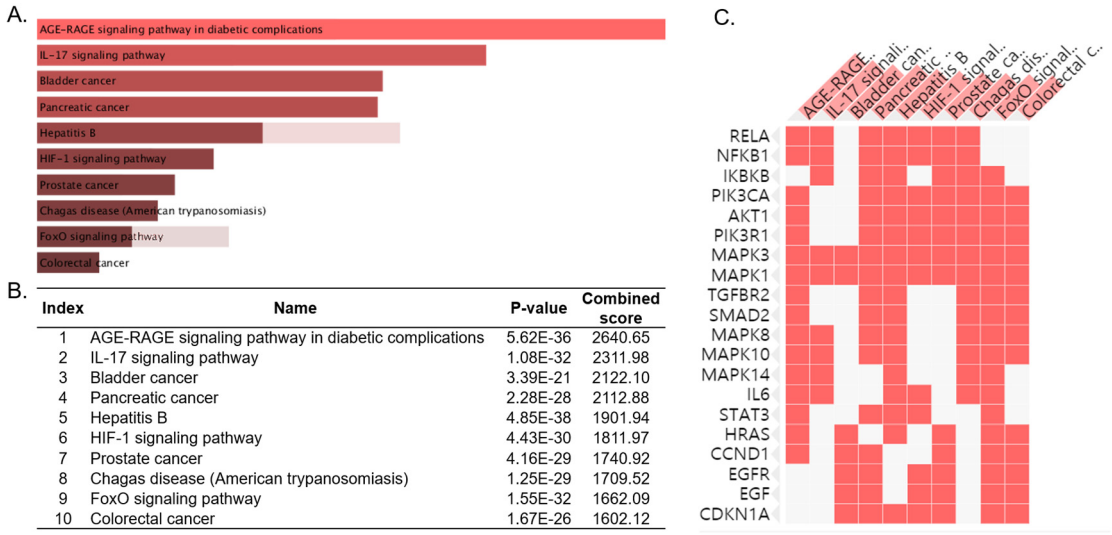
B.

Gene name	Protein name	Edges	Function (GO Biological Process)
AKT1	Proline-rich AKT1 substrate 1	99	negative regulation of cell size negative regulation of protein kinase activity
INS	Insulin	95	activation of protein kinase B activity acute-phase response
IL6	Interleukin 6	93	ciliary neurotrophic factor-mediated pathway cytokine-mediated signaling pathway
STAT3	Signal Transducer And Activator Of Tr anscription 3	90	cellular response to cytokine stimulus cellular response to hormone stimulus
TP53	Tumor Protein P53	85	autophagy bone marrow development
JUN	Transcription factor AP-1	79	aging angiogenesis
VEGFA	Vascular Endothelial Growth Factor A	79	activation of protein kinase activity artery morphogenesis
MAPK8	Mitogen-Activated Protein Kinase 8	78	cellular response to amino acid starvation cellular response to cadmium ion
TNF	Tumor necrosis factor	77	activation of cysteine-type endopeptidase activity involved in apoptotic process
MAPK1	Mitogen-activated protein kinase 1	76	activation of MAPK activity activation of MAPKK activity

Figure 1. The network analysis for LJ. (**A**) LJ network consisting of 359 nodes and 2891 edges. (**B**) Top 10 genes in the LJ network, with the highest edge degrees. Gene name, protein name, edges and functions are detailed.

3.2. Functional Enrichment Analysis of the LJ Network

Functional enrichment analysis was conducted to investigate the LJ network to identify specific pathways. As a result of the enrichment analysis, the top 10 pathways related to the network were gathered: 'Advanced glycation end products-Receptor for advanced glycation end products (AGE-RAGE) signaling pathway in diabetic complications', 'Interleukin 17 (IL-17) signaling pathway', 'Bladder cancer', 'Pancreatic cancer', 'Hepatitis B', 'Hypoxia-inducible factor 1-alpha (HIF-1) signaling pathway', 'Prostate cancer', 'Chagas disease', 'Forkhead box transcription factors (FoxO) signaling pathway', 'Colorectal cancer' (Figure 2A). 'AGE-RAGE signaling pathway in diabetic complications' was predicted to be the most relevant pathway to LJ, with the lowest *p*-value (5.62×10^{-36}) and the highest combined score (2640.65), both representing confidence in the correlation (Figure 2B). *RELA*, *NFKB1*, *PIK3CA*, *AKT1*, *PIK3R1*, *MAPK3*, *MAPK1*, *TGFBR2*, *SMAD2*, *MAPK8*, *MAPK10*, *MAPK14*, *IL6*, *STAT3*, *HRAS* and *CCND1* were found to be genes related to both 'AGE-RAGE signaling pathway in diabetic complications' and the network of LJ (Figure 2C). 'IL-17 signaling pathway' and 'Bladder cancer' were presented with *p*-values of 1.08×10^{-32} and 3.39×10^{-21} and combined scores of 2311.98 and 2122.10, respectively.



Index	Name	P-value	Combined score
1	AGE-RAGE signaling pathway in diabetic complications	5.62E-36	2640.65
2	IL-17 signaling pathway	1.08E-32	2311.98
3	Bladder cancer	3.39E-21	2122.10
4	Pancreatic cancer	2.28E-28	2112.88
5	Hepatitis B	4.85E-38	1901.94
6	HIF-1 signaling pathway	4.43E-30	1811.97
7	Prostate cancer	4.16E-29	1740.92
8	Chagas disease (American trypanosomiasis)	1.25E-29	1709.52
9	FoxO signaling pathway	1.55E-32	1662.09
10	Colorectal cancer	1.67E-26	1602.12

Figure 2. Functional enrichment analysis of the LJ network, with combined scores in descending order. (**A**) Bar graph showing the pathways and their combined scores. (**B**) Pathways detailed with *p*-values and combined scores. (**C**) A clustergram of related genes.

3.3. Specific Mechanisms of LJ in the AGE-RAGE Signaling Pathway in Diabetic Complications

For the purpose of discovering more specific mechanisms of LJ, a gene comparison for the LJ network and 'AGE-RAGE signaling pathway in diabetic complications' was undertaken (Figure 3A). Among the genes in the LJ network, 34 genes were in common with the genes in the 'AGE-RAGE signaling pathway in diabetic complications' pathway (Figure 3B). On a map of the pathway (KEGG pathway: hsa04933), the common genes were marked in red and the paths of the marked genes were highlighted in yellow (Figure 4). Among the 'AGE-RAGE signaling pathway in diabetic complication' genes, LJ genes were found to be particularly associated with 'Mitogen-activated protein kinase (MAPK) signaling pathway' (*ERK1/2, P38, AP1, P21RAS, JNK, NFKB, MCP1, PAI1, VCAM1, MMP2, IL1, IL6, IL8, TNFA, THBD*), 'Phosphatidylinositol 3 kinase-Protein kinase B (PI3K-AKT) signaling pathway' (*NADPH, PI3K, AKT, NOS, JNK, P38, FOXO1, CASP3*) and 'Janus kinase-Signal transducers and activators of transcription (JAK-STAT) signaling pathway' (*JAK2, STAT3, STAT1, NFATC1, COL1, CYCD1, CDK4*).

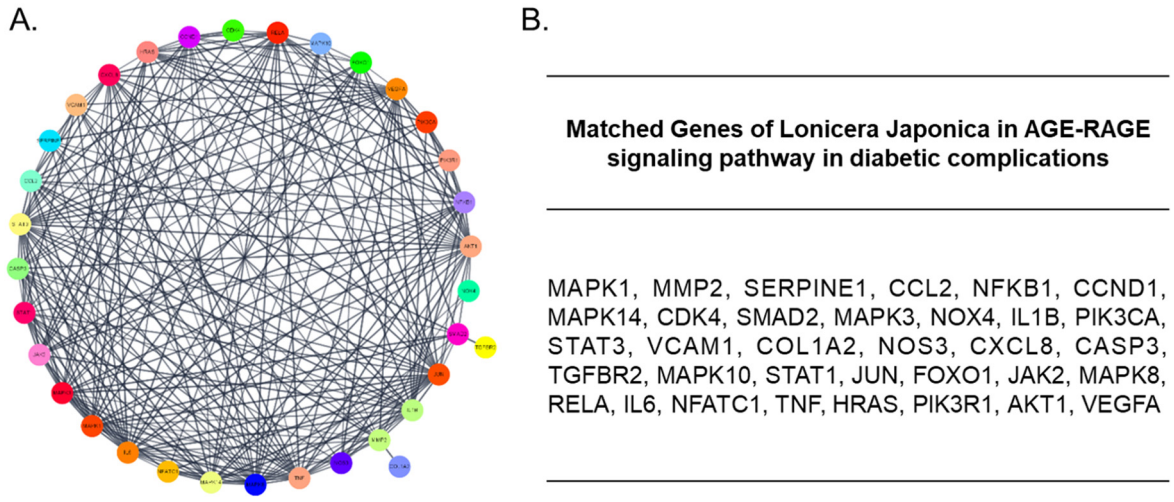


Figure 3. (**A**) The LJ network consisting of 34 nodes and 543 edges. (**B**) LJ genes matched with genes in the AGE-RAGE signaling pathway in the diabetic complications network (34 matched genes in total).

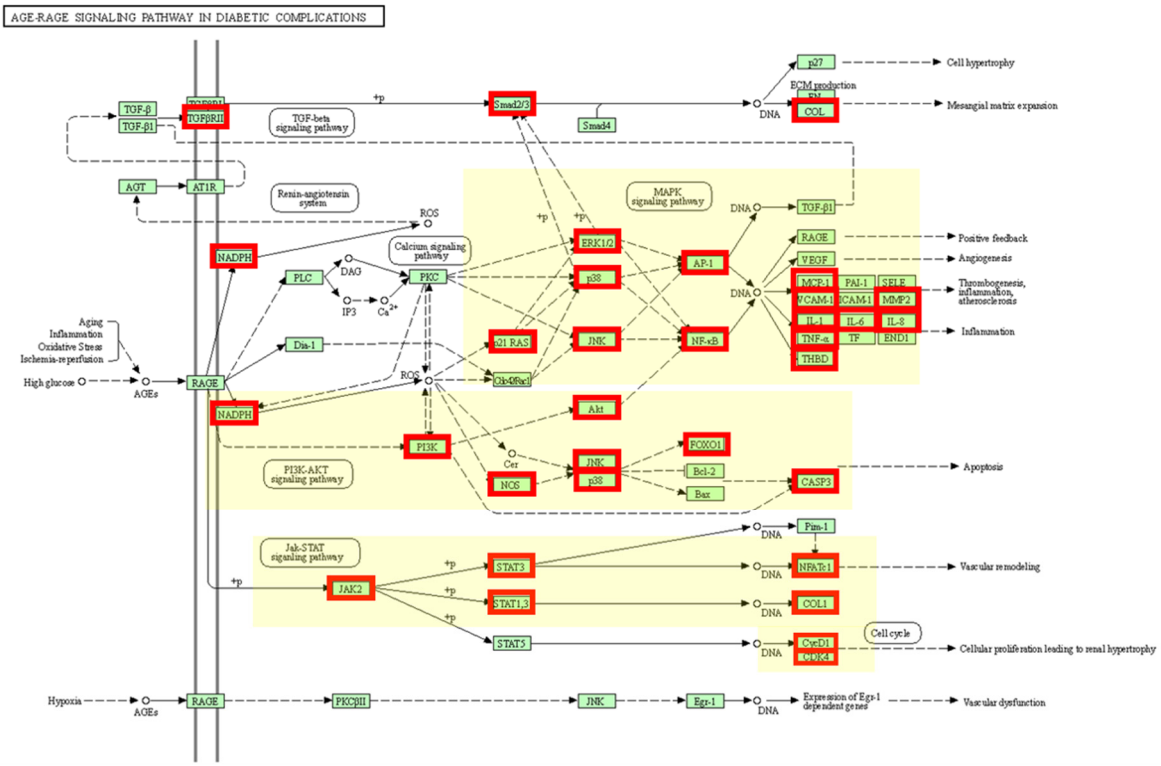


Figure 4. A diagram of the AGE-RAGE signaling pathway in diabetic complications. KEGG pathway: hsa04933. Matched genes are marked in red boxes.

4. Discussion

This study was designed to discover and predict the potential efficacy and mechanisms of LJ based on network pharmacology. Network pharmacology is known to be an analytical method which enables target genes to be gathered and network analyses to be performed to identify features of elements in a gene set. In the present study, 26 compounds of LJ were collected from the literature via open databases. Through public databases, such as PubChem, target genes of the compounds were used to build the network for LJ, which consists of genes and their connections. On the basis of the LJ network, the main target genes and potential pathways of LJ were investigated and 'AGE-RAGE signaling pathway in diabetic complications' emerged as the most relevant pathway for LJ with the lowest *p*-value and the highest combined score, both indicating confidence in the correlated pathway. In addition, 'IL-17 signaling pathway', 'Bladder cancer', 'Pancreatic cancer', 'Hepatitis B', 'HIF-1 signaling pathway', 'Prostate cancer', 'Chagas disease', 'FoxO signaling pathway' and 'Colorectal cancer' can also be predicted as potential mechanisms of LJ.

Among the targets of the LJ network, the top 10 targets with the highest edges were presented in order of high edge degrees. *AKT1* was the node with the highest number of edges, associating with 99 other genes in the network. GO Biological Process is a database which provides computational analyses of large-scale molecular biology and genetics experiments in biomedical research. Based on GO Biological Process, known functions of *AKT1* were derived. As *AKT1* was the node with the highest edges, 'negative regulation of cell size' and 'negative regulation of protein kinase activity' functions of *AKT1* can be predicted as functions of LJ.

Through functional enrichment analysis, the gene set for LJ was analyzed to predict potential pathways of LJ. 'AGE-RAGE signaling pathway in diabetic complications' was identified as the pathway most highly correlated with the LJ network based on functional enrichment analysis. This result suggests that the AGE-RAGE pathway might be a potential mechanism of LJ and that LJ might have therapeutic efficacy in relation to diabetic complications. Genes including *AKT1*, *IL6*, *STAT3* and *MAPK1* were associated with the

AGE-RAGE signaling pathway, which implies that the top 10 edge degree genes of the network are highly related to the main pathway of LJ. Not only 'AGE-RAGE signaling pathway in diabetic complications' but also other pathways, including 'IL-17 signaling pathway', can be predicted as related mechanisms of LJ.

The 34 genes in common between the LJ network and 'AGE-RAGE signaling pathway in diabetic complications' were extracted. Among the common genes, *ERK1/2*, *P38*, *AP1*, *P21RAS*, *JNK*, *NFKB*, *MCP1*, *PAI1*, *VCAM1*, *MMP2*, *IL1*, *IL6*, *IL8*, *TNFA* and *THBD* belonged to 'MAPK signaling pathway'. *NADPH*, *PI3K*, *AKT*, *NOS*, *JNK*, *P38*, *FOXO1* and *CASP3* belonged to 'PI3K-AKT signaling pathway'. *JAK2*, *STAT3*, *STAT1*, *NFATC1*, *COL1*, *CYCD1* and *CDK4* belonged to 'JAK-STAT signaling pathway'. The results demonstrated that LJ might affect the 'AGE-RAGE signaling pathway in diabetic complications' pathway in humans through 'MAPK signaling pathway', 'PI3K-AKT signaling pathway' and 'JAK-STAT signaling pathway'. In order to confirm whether the results were reliable, the relevance of LJ to 'MAPK', 'PI3K-AKT' and 'JAK-STAT' was investigated based on literature studies. LJ attenuated H2O2-induced apoptosis by blocking the phosphorylation of PI3K/Akt and MAPKs [17]. LJ down-regulated the production of pro-inflammatory mediators, including nitric oxide (NO), as well as pro-inflammatory cytokines (IL-1β and TNF-α) by suppressing nuclear factor-kappa B (NF-kB) activity at least through inhibition of the PI3K-Akt signaling pathway [26]. LJ inhibits LPS-stimulated phosphorylation of MAPKs, PI3K/Akt and Jak-STAT as well as the activation of NF-kB p65 [27].

The therapeutic effects of LJ regarding diabetes and diabetic complications were investigated on the basis of previous reports. In our previous study, oral administration of LJ ameliorated damaged β-islet cells in the pancreas by inhibiting peroxisome proliferator-activated receptor-γ in type 2 diabetic rats [28]. Another study showed that LJ ethanolic extract improved diabetic nephropathy via inhibition of p38-mediated inflammatory response in rats [29]. Additionally, hypoglycemic and hypolipidemic effects of polysaccharides from LJ flower buds have been reported [30]. Taken together, the results in this study correspond well with those found in the literature on LJ. Given this, the network pharmacology-based study of LJ can be regarded as a proper prediction method, providing consistent results.

In conclusion, LJ might have promising effects on 'AGE-RAGE signaling pathway in diabetic complications' based on the network analysis undertaken here, and this result was consistent with the results of previous studies. This study suggests that network pharmacological analysis can be an appropriate method for LJ investigation and provides predictions of therapeutic efficacy and mechanisms of LJ.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app12189122/s1, Table S1: Targets of compounds in *Lonicera Japonica* Thunberg.

Author Contributions: Conceptualization, S.J.P. and W.M.Y.; methodology, S.J.P.; formal analysis, S.J.P. and M.H.K.; investigation, S.J.P. and M.H.K.; data curation, W.M.Y.; writing—original draft preparation, S.J.P.; writing—review and editing, S.J.P. and M.H.K.; visualization, S.J.P.; supervision, W.M.Y.; project administration, W.M.Y.; funding acquisition, W.M.Y. All authors have read and agreed to the published version of the manuscript.

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