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Comment:
The paper does not meet the standards of "Chinese Medicine ".

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Editor guiding this retraction: Prof. Maythem Saeed (EiC of CM)

Exploring the Mechanism of Wu Ling San plus Flavor for the Treatment of Diabetic Macular Edema Based on Network Pharmacology and Molecular Docking Techniques

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Abstract

Aim: To explore the possible mechanism of action of Wu Ling San Plus for the treatment of diabetic macular edema (DME) through network pharmacology and molecular docking. Methods: DME-related genes were searched in drugbank database, GeneCards database, Online Mendelian Human Genetic (OMIM) database, and TTD database. The Traditional Chinese Medicine Systems Pharmacology (TCMSP) database was applied to screen for potential chemically active substances and related target proteins in the drug pairs. A "drug-disease target" regulatory network was constructed with Cytoscape (3.7.2) software, and a protein-protein interaction (PPI) network was established by Bisogenet and CytoNCA, followed by GO and KEGG enrichment analysis using the Bioconductor platform and R software. Finally, molecular docking of potential chemically active substances and key targets was performed using MOE software. Results: 63 compounds were screened from Wu Ling San Plus, including 71 targets for the treatment of DME, and the PPI core genes were AKT1, JUN, TP53, IL10, VEGFA, IL6, MMP9, CASP3, CCL2, PTGS2, MAPK8; GO biofunctional analysis contained 2143 enrichment results, mainly involving the hypoxic responses, the KEGG enrichment yielded 122 related signaling pathways consisting of the AGE-RAGE signaling pathway, cellular senescence pathway, TNF signaling pathway, IL-17 signaling pathway, C-type lectin receptor signaling pathway, FoxO signaling pathway, MAPK signaling pathway, T cell receptor signaling pathway, etc. Molecular

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docking results indicated that quercetin may have an effect on AKT1, TPP53, VEGFA, IL6, MMP9, CASP3, CCL2, PTGS2, and kaempferol also had a better binding ability to MAPK8. Conclusion: The treatment of DME with Wu Ling San Plus shows the multi-component and multi-target features of traditional Chinese medicine, which may achieve the management of DME's developing process through many routes, offering certain insights and a foundation for further research.

Keywords

Diabetic Macular Edema, Diabetic Retinopathy, Wu Ling San plus Flavor, Alkaloids, Aliphatic, Network Pharmacology, Molecular Docking

1. Background

Diabetic macular edema (DME) currently is the primary cause [1]. The prevalent pathogenesis of DME is a disruption in the production and absorption of fluid in the retina, leading to increased accumulation of fluid between the layers of the retina, with exudate accumulating in the macula. The disruption of the Blood-Retinal Barrier caused by an increase in the Vascular Endothelial Growth Factor is regarded to be the fundamental pathophysiology of DME (VEGF). Anti-VEGF injections are the most frequent treatment for DME, however, due to variances in staging, severity, and the complexity of the concomitant retinal diseases, some patients have poor outcomes and the oedema is difficult and recurring to remove [2].

"Treatise on Typhoid Fever—Defining the Pulses and Symptoms of Sun Diseases," by Wu Ling San. Only five plants are used in the original formula: Oriental Waterplantain rhizome, Polyporus, Atractylodes, Poria, and Cassia twig, which have the effects of warming yang, transforming qi, promoting water and permeating dampness, and are mainly used to treat the evidence of stagnation of water and dampness in the bladder, thus primary being used in modern times for the evidence of internal stagnation of water and dampness [3]. According to traditional Chinese medicine, the yellowish color of macula is ascribed to the spleen evidence, which prefers dryness and despises dampness, so if water and dampness cease inside the macula for an extended period of time, the middle yang will be obstructed, the spleen will be blocked, the spleen will be unable to transfer fluid, the qi will be weak, the water will flood and produce swelling, and the water and dampness will halt in the macular area, causing macular edema. Treatment for DME patients with long-term diabetes mellitus should include systemic and fundus identification, as well as the principles of nourishing yin and benefitting qi, as well as dipping dampness and strengthening the spleen [4] [5] [6].

The Wu Ling San formula was supplemented with *Rehmannia glutinosa* to nourish Yin and promote fluid, Milkvetch root to strengthen the spleen, tonify

Qi, and promote diuresis to reduce swelling, and fried Coix seed to strengthen the effect of diuresis and dampness to strengthen the spleen in this study. However, the target and mechanism of action remain unknown. Network pharmacology provides a comprehensive explanation of the pharmacological mechanisms underlying drug formulations, enabling time and labor-efficient enhancement of clinical efficacy as well as reduction of toxicity and side effects [7]. Additionally, molecular docking is a theoretical method to study the interaction and recognition between protein receptors and small molecule ligands owing to its capacity to predict the binding mode and affinity strength [8] [9] [10]. Network pharmacology, as a brand new subject based on system biology, bioinformatics, and high throughput histology, is getting more and more motivated [11] [12] [13]. Therefore, this study employed network pharmacology combined with molecular docking to explore the key genes and pathogenesis of Wu Ling San plus flavor for the treatment of DME, with the goal of identifying novel therapeutic targets.

2. Materials and Methods

2.1. Software and Databases

TCM Systematic Pharmacology Analysis Platform (TCMSP, http://tcmspw.com/tcmsp.php/);

Drugbank database (https://go.drugbank.com/);

NCBI Gene database (https://www.ncbi.nlm.nih.gov/gene/); GeneCards database (https://www.genecards.org/);

Online Mendelian Inheritance in Man (OMIM) database (http://www.omim.org/);

TTD database (http://db.idrblab.net/ttd/);

RCSB PDB database (http://www.rcsb.org/);

Cytoscape software (Version 3.7.2); Rgui software (Version 3.6.2); MOE software (Version 2015.10).

2.2. Methods

2.2.1. Screening for DME-Related Genes

DME-related targets were collected in the drugbank database, NCBI Gene database, GeneCards database, OMIM database, and TTD database, respectively, using the Diabetic Macular Edema keyword, and Merge was performed after removing duplicates.

2.2.2. Active Ingredient Screening and Target Prediction

TCMSP was used to screen the compounds for the activity of Polyporus, Atractylodes, Poria, Cassia twig, *Rehmannia glutinosa*, Milkvetch root, and Coix seeds using bioavailability (OB) and drug-like properties (DL). The activity screening was performed to select those that satisfied both OB ≥ 30% and DL ≥ 0.18 [14] as potential active ingredients. The TCMSP was then adopted to identify the active component targets in each herbal remedy.

2.2.3. Regulatory Network

The interaction targets, the prospective targets of action of Wu Ling San plus flavor on potential active ingredients associated with DME, and the disease differential genes acquired from the screening were compared and analyzed using Perl language. The compound names, target gene names, main biological functions, and signaling pathways were then imported into Cytoscape 3.7.2 software to map the regulatory network of Wu Ling San plus flavor.

2.2.4. Protein-Protein Interaction Network Construction

The identities of interacting target genes of drugs and diseases were imported into Cytoscape 3.7.2 software, and the Bisogenet package was installed to construct protein interaction (PPI) networks [15], followed by the CytoNCA package for network topology analysis.

2.2.5. GO Biofunctional Enrichment Analysis

The ID-transformed target genes acquired after network merging were then submitted to GO enrichment analysis using the Bioconductor platform and R software to assess the protein groups included in each GO annotation with a p-value and indicate the relevance of the protein biological functions. Biological process (BP), molecular function (MF), and cellular composition (CC) were selected. Bubble maps were plotted in 3 modules.

2.2.6. KEGG Metabolic Pathway Enrichment Analysis

The Bioconductor platform and R software were applied to perform KEGG metabolic pathway enrichment analysis on the target genes of drug-disease interaction to determine key metabolic pathways of action of Wu Ling San plus flavor for the treatment of DME.

2.2.7. Molecular Docking Validation

The chemical structures of the active ingredients of Wu Ling San plus flavor in mol2 format were obtained by searching in the TCMSP database, the protein crystal structures were obtained from the RCSB PDB database (http://www.rcsb.org/), and the original ligands or inhibitors of c-Jun, PPARG, NR3C1, RXRA, BCL2 were also searched. The MOE 2015.10 software was utilized for the chemical components with greater than average degree values in the active component-target of action network and the PPI network for c-Jun, PPARG, NR3C1, RXRA, BCL2 (c-JUN crystal structure PDB: 4W4V, PPARG crystal structure PDB: 3ADT, NR3C1 crystal structure PDB: 3ADT, NR3C1 crystal structure PDB: 4LSJ, RXRA crystal structure PDB: 3NSQ, BCL2 crystal structure PDB: 4IEH) were molecularly docked to obtain the corresponding docking data and the docking data of c-JUN, PPARG, NR3C1, RXRA, BCL2 with their original ligands or inhibitors. The value of binding energy was used to measure the docking impact between the active component and the primary target and the interactions between the drug molecules and protein crystals were analyzed by planar molecular interaction maps and three-dimensional interac-

tion pattern maps.

3. Results

3.1. Acquisition of DME-Related Targets

DME-related targets were collected from five databases, namely drugbank database, NCBI Gene database, GeneCards database, OMIM database, and TTD database with the Diabetic Macular Edema keyword, respectively, and 35, 33, 11, 905, and 17 DME-related targets were combined after removing duplicates to obtain a total of 957 DME-related targets.

3.2. Drug-Disease Target Prediction

From the TCMSP database, 31, 55, 34, 220, 87, 76, and 38 compounds were searched for Polyporus, Atractylodes, Poria, Cassia twig, *Rehmannia glutinosa*, Milkvetch Root, and Coix seeds, respectively, and 63 were finally selected based on bioavailability (OB) ≥ 30% and drug-like properties (DL) ≥ 0.18, derived from Polyporus with 11, atractylodes with 7, Poria with 15, Cassia Twig with 7, Milkvetch Root with 20, *Rehmannia glutinosa* with 2, and Coix seeds with 9, as shown in Table 1. The target proteins of the selected compounds were obtained from the TCMSP database, and their corresponding gene names were searched in the UniProt database, the DME-related genes got from the joint screening of related databases, and 61 genes were acquired from the intersection of the two, as shown in Figure 1.

3.3. Therapeutic DME Regulatory Network Construction

A drug compound-acting target disease network with 35 nodes was constructed using Cytoscape 3.7.2 software (Figure 2), in which purple, yellow, green, cyan, blue, red, and pink nodes represent the main active compounds of DME, C. multiflora, Poria, Cassia, Dioscorea, Astragalus, and Coix seeds, respectively, and blue nodes represent potential targets, with each edge indicating compound and target The interaction relationship between compounds and targets. It can be seen that MOL000098 (quercetin) and MOL000422 (kaempferol) play a key role in the whole network and may be the core compounds of the Angelica-Chuanxiong drug pair for the treatment of DME.
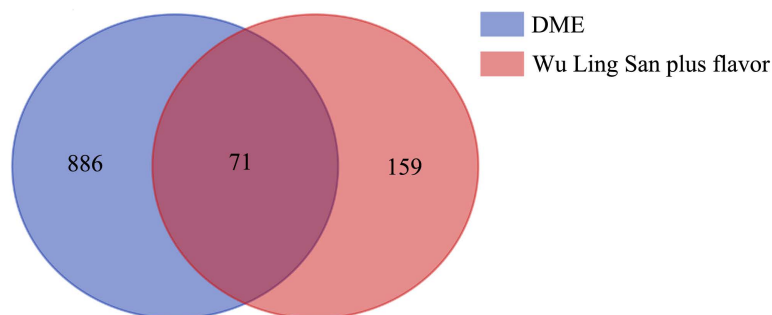

Figure 1. Venn diagram of Wu Ling San plus flavor and DME genes.

Table 1. 63 active compounds in Wuling powder with added flavor.

Number	Encoding	Name	OB/%	DL
1	MOL000020	12-senecioyl-2E,8E,10E-atractylentriol	62.40	0.22
2	MOL000021	14-acetyl-12-senecioyl-2E,8E,10E-atractylentriol	60.31	0.31
3	MOL000022	14-acetyl-12-senecioyl-2E,8Z,10E-atractylentriol	63.37	0.30
4	MOL000028	*α*-Amyrin	39.51	0.76
5	MOL000033	(24S)-24-Propylcholesta-5-Ene-3*β*-Ol	36.23	0.78
6	MOL000049	3*β*-acetoxyatractylone	54.07	0.22
7	MOL000072	8*β*-ethoxy atractylenolide III	35.95	0.21
8	MOL000073	ent-Epicatechin	48.96	0.24
9	MOL000098	quercetin	46.43	0.28
10	MOL000211	Mairin	55.38	0.78
11	MOL000239	Jaranol	50.83	0.29
12	MOL000273	16*α*-Hydroxydehydrotrametenolic acid	30.93	0.81
13	MOL000275	trametenolic acid	38.71	0.80
14	MOL000276	7,9(11)-dehydropachymic acid	35.11	0.81
15	MOL000279	Cerevisterol	37.96	0.77
16	MOL000280	(2R)-2-[(3S,5R,10S,13R,14R,16R,17R)-3,16-dihydroxy-4,4,10,13,14-pentamethyl-2,3,5,6,12,15,16,17-octahydro-1H-cyclopenta [a] phenanthren-17-yl]-5-isopropyl-hex-5-enoic acid	31.07	0.82
17	MOL000282	ergosta-7,22E-dien-3*β*-ol	43.51	0.72
18	MOL000283	Ergosterol peroxide	40.36	0.81
19	MOL000285	(2R)-2-[(5R,10S,13R,14R,16R,17R)-16-hydroxy-3-keto-4,4,10,13,14-pentamethyl-1,2,5,6,12,15, 16,17-octahydrocyclopenta [a]phenanthren-17-yl]-5-isopropyl-hex-5-enoic acid	38.26	0.82
20	MOL000287	3*β*-Hydroxy-24-methylene-8-lanostene-21-oic acid	38.70	0.81
21	MOL000289	pachymic acid	33.63	0.81
22	MOL000290	Poricoic acid A	30.61	0.76
23	MOL000291	Poricoic acid B	30.52	0.75
24	MOL000292	poricoic acid C	38.15	0.75
25	MOL000296	hederagenin	36.91	0.75
26	MOL000300	dehydroeburicoic acid	44.17	0.83
27	MOL000354	isorhamnetin	49.60	0.31
28	MOL000358	*β*-sitosterol	36.91	0.75
29	MOL000359	sitosterol	36.91	0.75

Continued

| 30	MOL000371	3,9-di-O-methylnissolin	53.74	0.48
31	MOL000374	5'-hydroxyiso-muronulatol-2',5'-di-O-glucoside	41.72	0.69
32	MOL000378	7-O-methylisomucronulatol	74.69	0.30
33	MOL000379	9,10-dimethoxypterocarpan-3-O-β-D-glucoside	36.74	0.92
34	MOL000380	(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano [3,2-c]chromen-3-ol	64.26	0.42
35	MOL000387	Bifendate	31.10	0.67
36	MOL000392	formononetin	69.67	0.21
37	MOL000398	isoflavanone	109.99	0.30
38	MOL000417	Calycosin	47.75	0.24
39	MOL000422	kaempferol	41.88	0.24
40	MOL000433	FA	68.96	0.71
41	MOL000438	(3R)-3-(2-hydroxy-3,4-dimethoxyphenyl)chroman-7-ol	67.67	0.26
42	MOL000439	isomucronulatol-7,2'-di-O-glucosiole	49.28	0.62
43	MOL000442	1,7-Dihydroxy-3,9-dimethoxy pterocarpene	39.05	0.48
44	MOL000449	Stigmasterol	43.83	0.76
45	MOL000492	(+)-catechin	54.83	0.24
46	MOL000796	(22E,24R)-ergosta-6-en-3β,5α,6β-triol	30.20	0.76
47	MOL000797	(22E,24R)-ergosta-7,22-dien-3-one	44.88	0.72
48	MOL000798	ergosta-7,22-diene-3β-ol	43.51	0.72
49	MOL000801	5α,8α-epidioxy-(22E,24R)-ergosta-6,22-dien-3β-ol	44.39	0.82
50	MOL000816	ergosta-7,22-dien-3-one	44.88	0.72
51	MOL000817	ergosta-5,7,22-trien-3-ol	46.18	0.72
52	MOL000820	polyporusterone E	45.71	0.85
53	MOL000822	polyporusterone G	33.43	0.81
54	MOL000953	CLR	37.87	0.68
55	MOL001323	Sitosterol α	43.28	0.78
56	MOL001494	Mandenol	42.00	0.19
57	MOL001736	(-)-taxifolin	60.51	0.27
58	MOL002372	(6Z,10E,14E,18E)-2,6,10,15,19,23-hexamethyltetracosa-2,6,10,14,18,22-hexaene	33.55	0.42
59	MOL002882	[(2R)-2,3-dihydroxypropyl] (Z)-octadec-9-enoate	34.13	0.30
60	MOL004576	taxifolin	57.84	0.27
61	MOL008118	Coixenolide	32.40	0.43
62	MOL008121	2-Monoolein	34.23	0.29
63	MOL011169	Peroxyergosterol	44.39	0.82
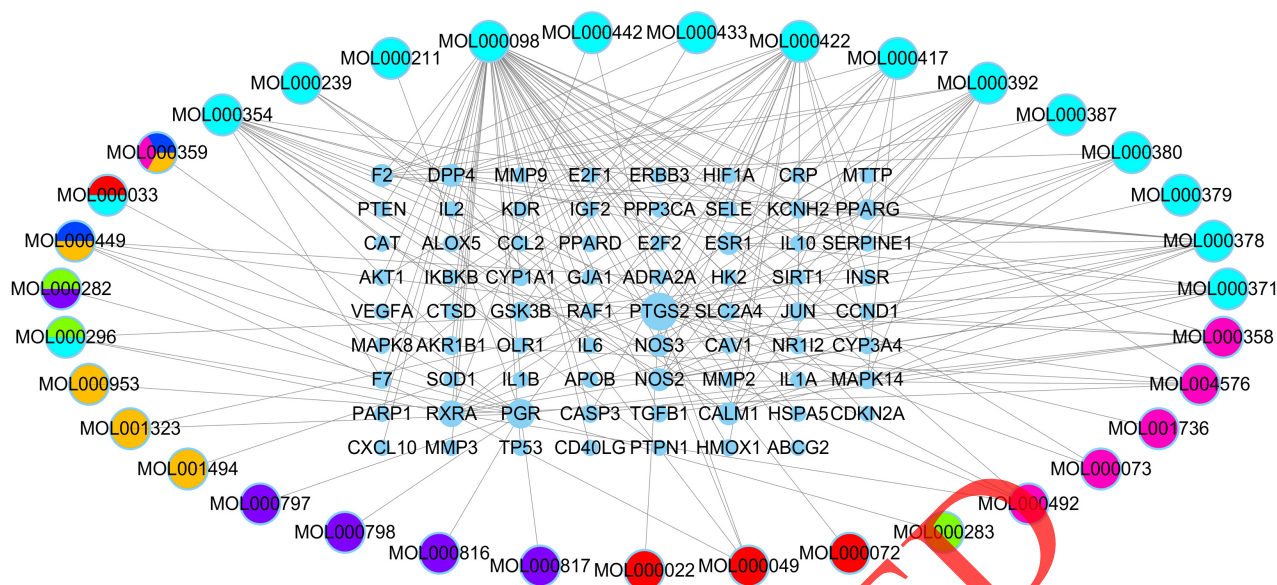
Figure 2. Drug-compounds-targets-disease network.

3.4. PPI Network Analysis

The 71 intersecting target genes obtained from drug-disease mapping were imported into the String database for PPI network analysis before the topological analysis was performed by CytoNCA in Cytoscape 3.7.2 (**Figure 3(a)**), showing the original 71 nodes, filtering the core network based on mediator closeness, degree, eigenvector, and LAC > median (**Figure 3(b)**), and then filtering the filtered network again until no more filtering is possible. The final screened network (**Figure 3(c)**) has 11 nodes and 55 edges, where the nodes represent proteins. From the final screened core network, it can be seen that AKT1, JUN, TP53, IL10, VEGFA, IL6, MMP9, CASP3, CCL2, PTGS2, MAPK8 play an important linkage role in the PPI network and may be the most important potential target of Wuling Sanga for the treatment of DME.

3.5. GO Enrichment Analysis

To further elucidate the possible roles of candidate targets, GO enrichment analysis was performed using the Bioconductor platform and R software, and 2143 GO entries were identified (p < 0.05). Among them, the largest number of entries related to biological processes (BP) with 2019 entries, mainly related to response to hypoxia, response to reduced oxygen levels, regulation of apoptotic signaling pathways, response to metal ions, regulation of DNA-binding transcription factor activity, regulation of reactive oxygen metabolic processes, cellular response to oxidative stress, and reproductive system development; molecular function (MF)-related entries with 92 entries, mainly in each GOs The top 20 entries with the highest P-values are presented in the form of a bar chart, see **Figure 4** indicating that the longer length represents a higher number of genes, indicating the higher importance of the entry.
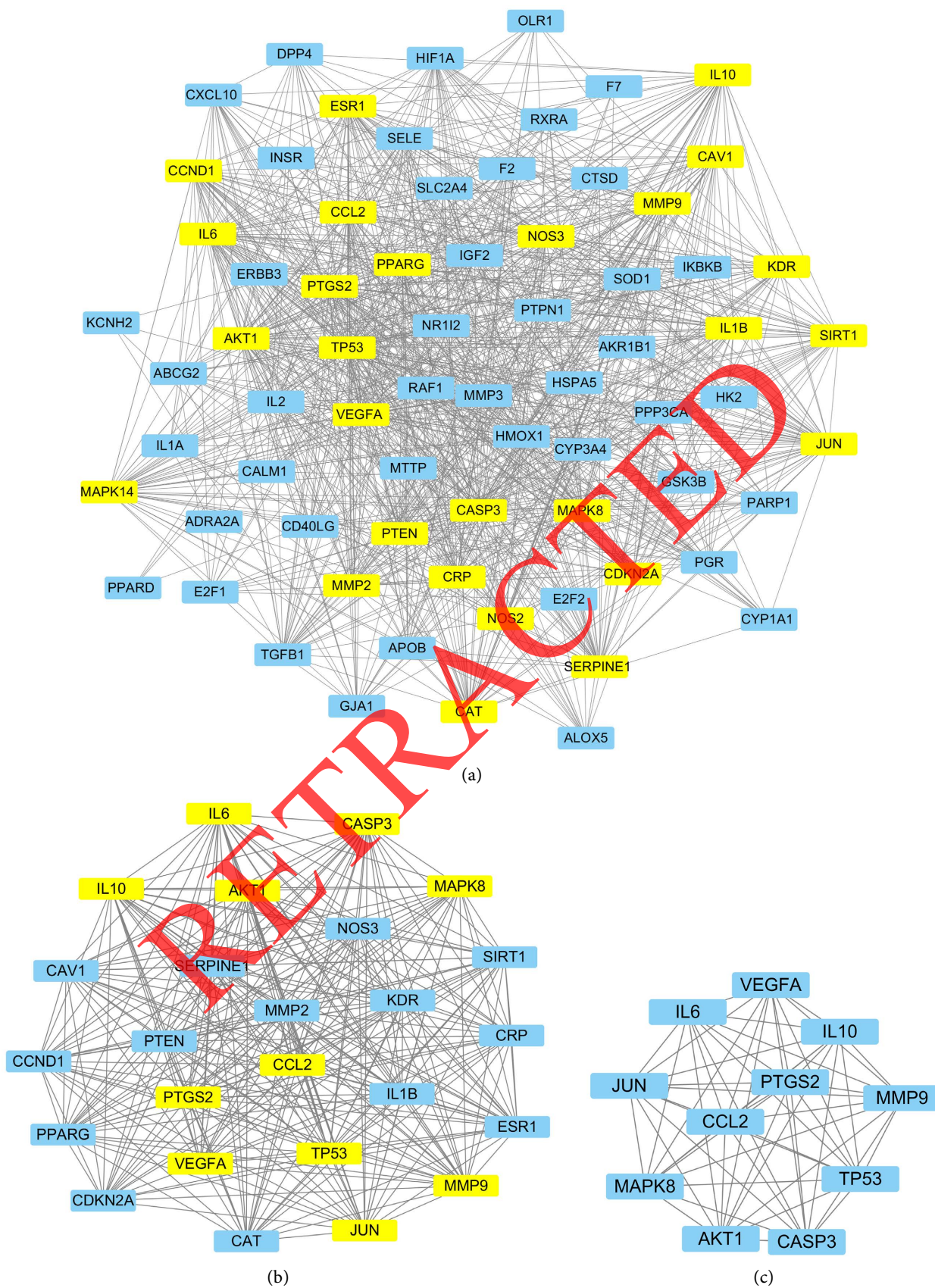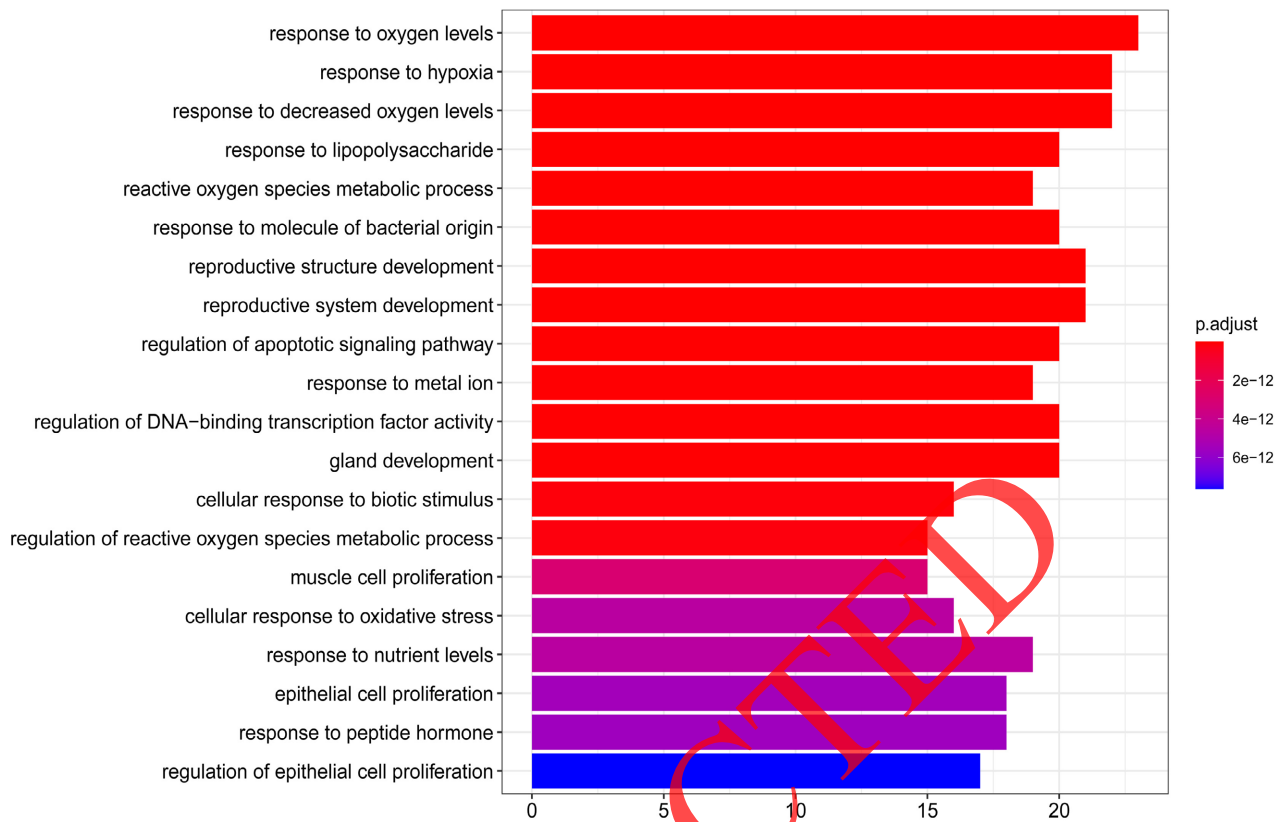
Figure 3. PPI network of Wu Ling San plus flavor and DME intersection targets.
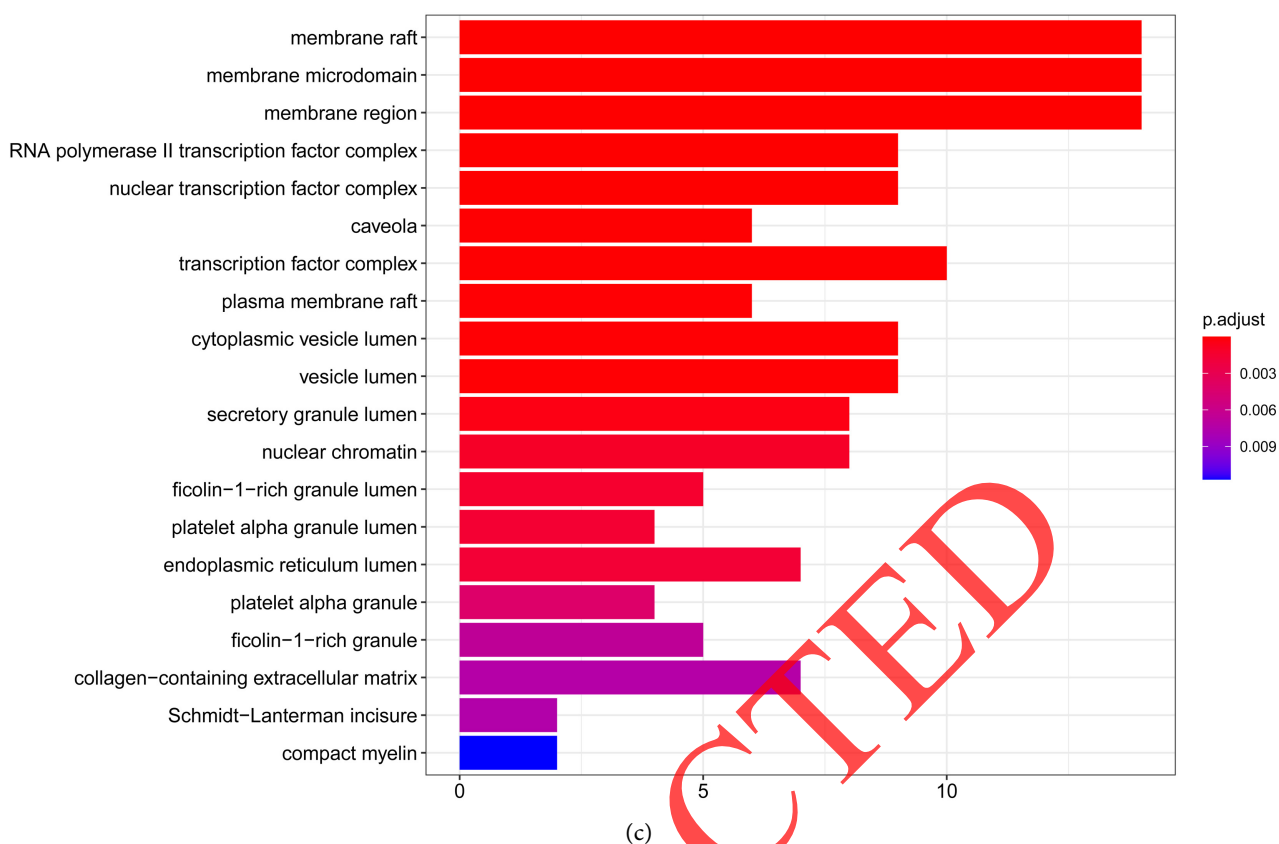
(a)

(b)

(c)

Figure 4. GO enrichment analysis. (a) Biological processes; (b) Molecular functions; (c) Cellular composition.

3.6. KEGG Enrichment Analysis

KEGG enrichment analysis was performed on 71 putative action targets using the Bio conductor platform and R language, yielding a total of 122 entries. The top 20 entries with small P-values are shown in **Figure 5**, which are presented in the form of bar graph plots. The length and color of the bar graph show significance; the greater the length, the more genes are represented, suggesting that the entry is more important. It can be seen that the relevant mechanisms mainly involve the AGE-RAGE signaling pathway, cellular senescence pathway, TNF signaling pathway, IL-17 signaling pathway, C-type lectin receptor signaling pathway, FoxO signaling pathway, MAPK signaling pathway, T cell receptor signaling pathway, etc.

3.7. Molecular Docking

The ligands in the proteins were isolated using Pymol (version 2.3.4), and the 11 proteins in **Figure 3(c)** were docked to quercetin and kaempferol compounds using AutoDock Vina, with binding energies (affinity) −7.0 kcal·mol⁻¹ indicating good binding activity [16] and the lower the binding energy, the better the docking is indicated. As shown in **Table 2**, a total of 2 out of 11 proteins have binding energy < −7.0 kcal·mol⁻¹ to the corresponding compounds, indicating that these proteins have a strong affinity for the compounds. **Figure 6** presents

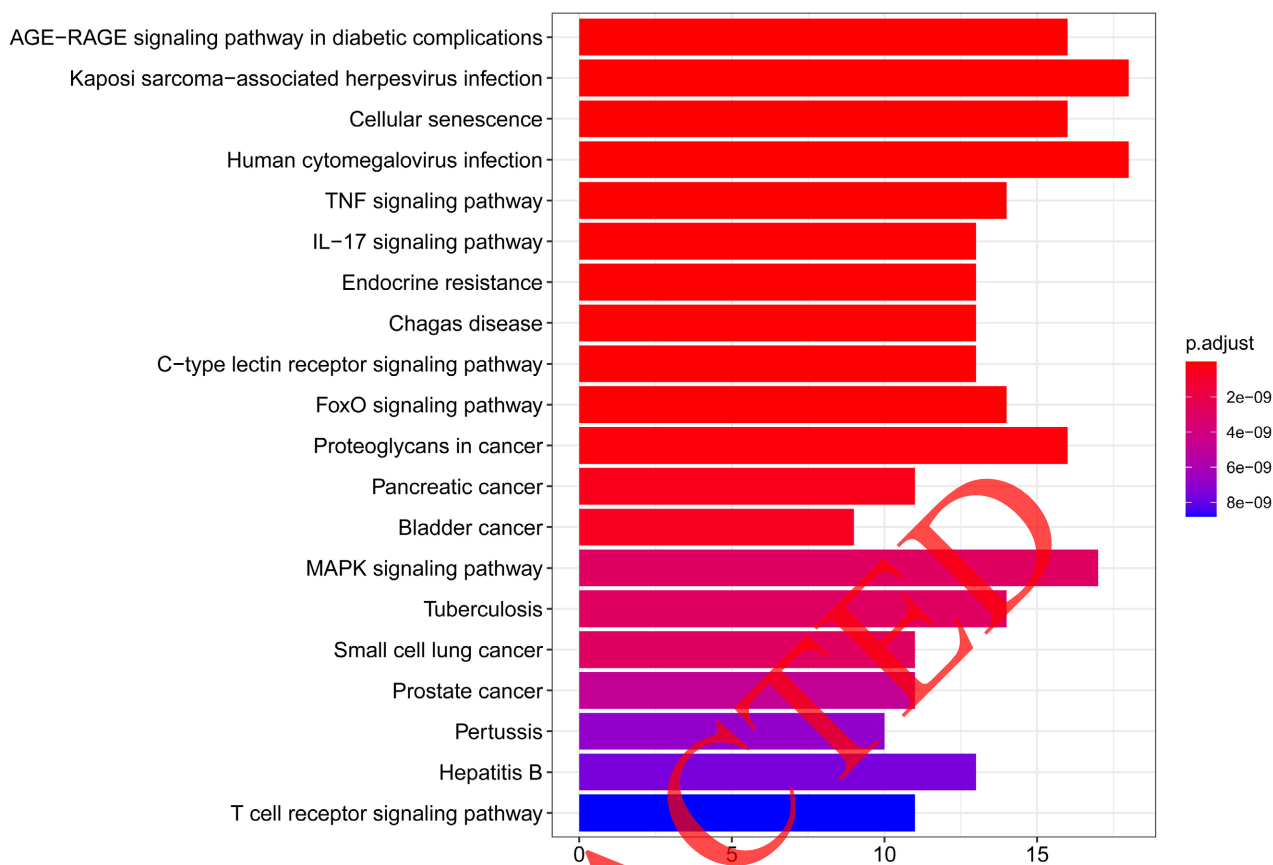**Figure 5.** KEGG pathway analysis.

(a)   (b)

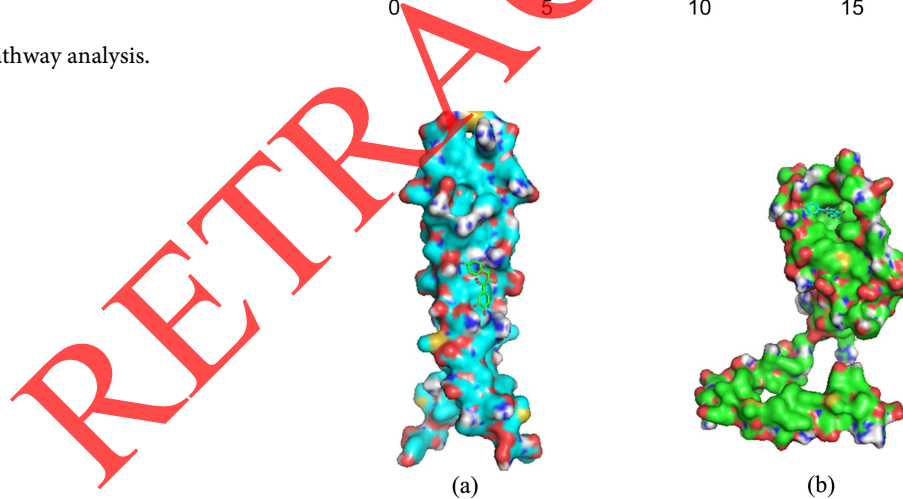**Figure 6.** Partial diagram of molecular docking: (a) JUN-quercetin; (b) IL-10-quercetin.

Table 2. Docking results of active compounds and potential targets.

Target point	Chemical compound	Binding energy/(kcal·mol^{-1})
JUN	quercetin	−5.5
IL10	quercetin	−6.7

the docking complex of the eleven targets together with their strongest binding components.

4. Discussion

Network pharmacology, which is based on the theory of systems biology, uses various methods such as histology and network visualization to create system network models to examine the intervention and impact of drugs on diseases from a holistic perspective and reveal the complex relationships between drugs, diseases, targets, and pathways, which are important for understanding the mechanism of action, the material basis of pharmacological effects, and the development of new drugs [17] [18] [19] [20] [21].

In the present study, TCM active component-target network analysis revealed that quercetin, kaempferol, and other active ingredients can act on multiple targets in the network. This data implies that these components are significant for Wu Ling San Plus's therapeutic impact on DME and should be investigated further. Quercetin has the most potential targets. According to previous reports, quercetin, one of the most prominent members of the natural flavonoid family, has been reported to be beneficial in age-related ophthalmopathy and retinal ischemia-reperfusion injury [22] [23], whose protective effect on retinopathy was mainly attributed to its anti-oxidative, anti-inflammatory, anti-apoptotic, anti-angiogenic and neuroprotective effects in retinal cells [24] [25] [26].

The main proteins of the PPI network, AKT1, JUN, VEGFA, MMP9, and CASP3, were evaluated in this study, revealing that the active components of Wu Ling San Plus had strong binding activity to them and can be exploited as prospective targets for the treatment of DME. Anti-VEGF therapy is currently a popular therapeutic option for DME. CASP3, a crucial executor downstream of the apoptotic pathway, performs a last executive function in the JUN apoptotic pathway [27] [28] [29]. MMPs are a family of Zn^{2+}-dependent endopeptidases that degrade all ECM components except polysaccharides, promote cell proliferation, neovascularization, and tissue remodeling, and MMP-9 is one of the most important members of the MMPs family, playing an essential role in the formation of DR.

The GO enrichment study produced intriguing findings and illustrated the complexity of DME pathogenesis. First, the target genes were found to be enriched in response to hypoxic stress, which may be directly influenced by sugar metabolism. Clinical and experimental studies have demonstrated that hyperglycemia is the primary factor leading to the pathogenesis of diabetic complications [30]. Oxidative stress can damage cell membrane integrity [31], nducing apoptosis, microvascular damage, and barrier damage and ultimately leading to DR development. 10 most important GO (BP) entries are mainly related to hypoxic response, oxygen level reduction response, apoptotic signaling pathway regulation, metal ion response, regulation of DNA-binding transcription factor activity, regulation of reactive oxygen metabolic processes, cellular oxidative stress response, and reproductive system development. Related studies have shown that the occurrence and development of DME are associated with cellular dysfunction and injury, chronic inflammatory infiltration, and oxidative stress [32] [33] [34] [35]. 92 molecular function (MF)-related entries, mainly related to

cytokine activity, nuclear receptor activity, ligand-activated transcription factor activity, steroid hormone receptor activity, growth factor receptor binding, etc; 32 entries related to cell composition (CC), mainly associated with membrane rafts, transcription factor complexes, endoplasmic reticulum lumen, etc.

KEGG metabolic pathway shows that its mechanism of action is mainly related to the AGE-RAGE signaling pathway, cellular senescence pathway, TNF signaling pathway, IL-17 signaling pathway, C-type lectin receptor signaling pathway, FoxO signaling pathway, MAPK signaling pathway, T cell receptor signaling pathway. The pathogenesis of DME is complex, which was linked to the breakdown of the inner BRB, as well as the malfunctioning of Müller cells and RPE. Müller cell, like a pump, drains ions and water into the vitreous body and retinal blood vessels with the support of normal distribution and function of Kir4.1 and AQP4. Müller cells, also the major glial cells in the retina, play a critical role in maintaining the structure and normal functions of the retina with highly expressed RAGE [36]. In addition, a study demonstrated that RAGE is of great significance in retinal neurodegeneration induced by diabetes and that early induction of RAGE expression by hyperglycemia in retinal Müller cells contributes to the increased levels of proinflammatory cytokines, including VEGF (a crucial downstream growth factor in angiogenesis) and monocyte chemoattractant protein-1 (MCP-1), both *in vivo* and *in vitro* [37]. Another common and well-known pathway, the TNF signaling pathway, is closely related to inflammation, which is a crucial process in DME progression [38]. Gao's study revealed that hypoxia inducible factor subtype 1α in diabetic retina is likely to play a role in dysfunction and vulnerability related to DR progression via TNF-α [39].

5. Conclusion

The treatment of DME with Wu Ling San Plus shows the multi-component and multi-target features of traditional Chinese medicine, which may achieve the management of DME's developing process through many routes, offering certain insights and a foundation for further research.

Authors' Contributions

Yanli Liu and Meixia An had full access to all study data and take responsibility for its integrity and the accuracy of the analysis. Kunmao Ke, Xiaoyun Jiang and Yun Zhang were responsible for the study concept and design. Yekai Zhou, Jian Zhao and Junbiao Zhang responsible for data acquisition, extraction and drafting the paper, which was revised by Yanli Liu and Meixia An. Yanli Liu and Meixia An supervised the study. All authors read and approved the final manuscript.

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from

the corresponding author on reasonable request.

Conflicts of Interest

The authors declare no competing interests regarding the publication of this manuscript.

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Abbreviations

TCMSP: Traditional Chinese Medicine System Pharmacology Database and Analysis Platform;

GO: Gene Ontology;

KEGG: Kyoto Encyclopedia of Genes and Genomes;

OB: Oral Bioavailability;

DL: Drug-Likeness.