Study on the Anti-Periodontitis Mechanism of Eucommia ulmoides Based on Network Pharmacology

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Abstract. Periodontitis is a chronic inflammation of periodontal support tissue caused by local factors. Eucommia ulmoides, a traditional Chinese medicinal herb, has a significant therapeutic effect on periodontitis, but its mechanism of action is still unclear. In this study network pharmacology method was used to deeply elucidate the pharmacological substance basis and mechanism of Eucommia ulmoides in treating periodontitis. The protein interaction network (PPI) was constructed using the STRING database. The GO and KEGG signal pathway enrichment analyses of the intersected targets were performed using the DAVID database to predict the mechanism of action. The results indicate that Eucommia ulmoides exerted its therapeutic effect on periodontitis through a synergistic mechanism of multiple components, targets, and pathways. The top 8 therapeutic targets were identified, including EGFR, HIF1A, MMP9, ESR1, JUN, PPARG, AKT1, and SRC. Prolactin and HIF-1 signaling pathway may be the key mechanism of Eucommia ulmoides in treating periodontitis.

Keywords: Eucommia ulmoides; network pharmacology; periodontitis.

1. Introduction

Periodontitis is a chronic inflammatory disease characterised by invasion of the periodontal soft and hard tissues, which clinically manifests as gingival bleeding, periodontal pocket formation, alveolar bone resorption and tooth loosening[1,2]. With the modernization and nationalization of traditional Chinese medicine (TCM), it is expected to become an effective way to treat periodontitis. Eucommia ulmoides, as a traditional anti-inflammatory Chinese medicine, has been recognized for its role in the treatment of periodontitis. The Compendium of Materia Medica provides a more detailed description of the origin and efficacy of Eucommia ulmoides. Modern research shows that the chemical components of Eucommia ulmoides mainly include phenylpropanoids, terpenoids, flavonoids, phenolic acids, steroids, and polysaccharides, which have anti-inflammatory and antioxidant pharmacological effects. They are often used alone or in combination to treat various diseases[3,4]. In this study, the material basis and mechanism of action of Eucommia ulmoides against periodontitis were investigated based on network pharmacology to predict its anti-periodontitis active components, targets and related pathways, and to provide more theoretical basis for the development of anti-periodontitis TCM.

2. Methods

2.1 Screening of the main active components of Eucommia ulmoides

The TCMSP (http://tcmspw.com/tcmsp.php), a systematic pharmacological database of Chinese medicines, was used to obtain the most important active ingredients by screening with the two conditions of oral bioavailability (OB) ≥ 30% and drug likeness (DL) ≥ 0.18.

2.2 Acquisition of disease-related genes for major components

The SMILE names of the screened compounds were obtained from the PubChem database. The SMILE name of the lead compound was imported into the Swiss Target Predictiondatabase, and the

target and its corresponding gene name were obtained, and the duplicate gene names were integrated and deleted.

2.3 Collection and screening of periodontitis-related targets

GeneCards, OMIM, PharmGKB, TTD and Disgent were searched for periodontitis-related targets using the keyword "periodontitis". The target information obtained from the five databases was imported into an Excel spreadsheet and merged, and duplicates were removed. The targets of Eucommia ulmoides were imported into the online mapping platform Venny 2.1.0 to obtain the drug-disease target intersection, and the potential targets of Eucommia ulmoides against periodontitis were obtained.

2.4 Construction of frug- ingredient-target diagram

The Cytoscape 3.10.1 software was used to construct drug- ingredient-target diagram to investigate the mechanism of action of Eucommia ulmoides against periodontitis.

2.5 Establishment of a network for Protein-Protein interaction (PPI)

The overlapping targets of Eucommia ulmoides and periodontal diseases were imported into the String database, the protein species was set to "Homo sapiens", the target proteins not connected to the network were hidden, and PPIs were constructed.

2.6 GO and KEGG signalling pathway enrichment analysis

The overlapping targets of Eucommia ulmoides and periodontal diseases were imported into the DAVID database, and the gene species were set as human genes, which were subjected to GO and KEGG enrichment analyses to analyse the biological process of anti-periodontal inflammation of Eucommia ulmoides and related signal pathways.

3. Results

3.1 Screening of active components of Eucommia ulmoides

A total of 28 active components of Eucommia ulmoides were obtained using OB ≥ 30% and DL ≥ 0.18 as screening conditions, through TCMSP database. The results are shown in table 1.

Table 1. Active Ingredients of Eucommia ulmoides

Mol ID	Molecule Name	MW	OB（%）	DL（%）
MOL000073	ent-Epicatechin	290.29	48.96	0.24
MOL000098	quercetin	302.25	46.43	0.28
MOL000211	Mairin	456.78	55.38	0.78
MOL000358	beta-sitosterol	414.79	36.91	0.75
MOL000422	kaempferol	286.25	41.88	0.24
MOL000443	Erythraline	297.38	49.18	0.55
MOL002058	40957-99-1	388.45	57.2	0.62
MOL002773	beta-carotene	536.96	37.18	0.58
MOL004367	olivil	376.44	62.23	0.41
MOL005922	Acanthoside B	580.64	43.35	0.77
MOL006709	AIDS214634	374.42	92.43	0.55
MOL007059	3-beta-Hydroxymethyllenetanshiquinone	294.32	32.16	0.41
MOL007563	Yangambin	446.54	57.53	0.81
MOL008240	(E)-3-[4-[(1R,2R)-2-hydroxy-2-(4-hydroxy-3-methoxy-phenyl)-1-methylol-ethoxy]-3-methoxy-phenyl]acrolein	374.42	56.32	0.36

MOL009007	Eucommin A	550.61	30.51	0.85
MOL009009	(+)-medioresinol	388.45	87.19	0.62
MOL009015	(-)-Tabernemontanine	354.49	58.67	0.61
MOL009027	Cyclopamine	411.69	55.42	0.82
MOL009029	Dehydrodiconiferyl alcohol 4,gamma'-di-O-beta-D-glucopyanoside_qt	358.42	51.44	0.4
MOL009030	Dehydrodieugenol	326.42	30.1	0.24
MOL009031	Cinchonan-9-al, 6'-methoxy-, (9R)-	324.46	68.22	0.4
MOL009038	GBGB	550.57	45.58	0.83
MOL009042	Helenalin	262.33	77.01	0.19
MOL009047	(+)-Eudesmin	386.48	33.29	0.62
MOL009053	4-[(2S,3R)-5-[(E)-3-hydroxyprop-1-enyl]-7-methoxy-3-methylol-2,3-dihydrobenzofuran-2-yl]-2-methoxy-phenol	358.42	50.76	0.39
MOL009055	hirsutin_qt	345.35	49.81	0.37
MOL009057	liriodendrin_qt	450.48	53.14	0.8
MOL011604	Syringetin	346.31	36.82	0.37

3.2 Construction of drug- ingredient-target network

The potential 185 intersection targets of Eucommia ulmoides for anti periodontitis and their corresponding active ingredients, as well as traditional Chinese medicine, were imported into the Catalscape 3.10.1 software for visualization, forming a drug- ingredient-target network (Fig. 1).

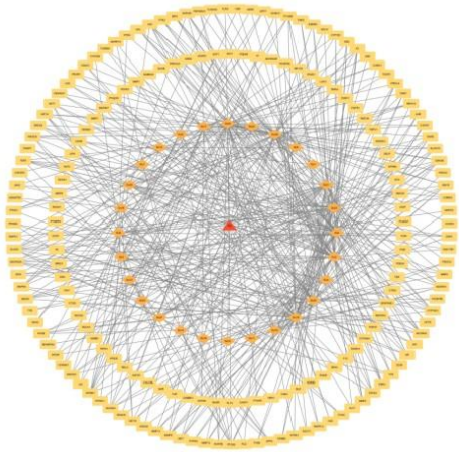

Fig. 1 Drug- ingredient-target diagram of the anti-Periodontitis effect of Eucommia ulmoides

3.3 Anti-periodontitis Protein-Protein interaction work of Eucommia ulmoides

The protein targets with the top 8 degree values in the PPI network were screened out and used as the core targets, which were EGFR, HIF1α, PPARα, PPARG, SRC, AKT1,MMP9, ESRP1 and JUN (Fig. 2).

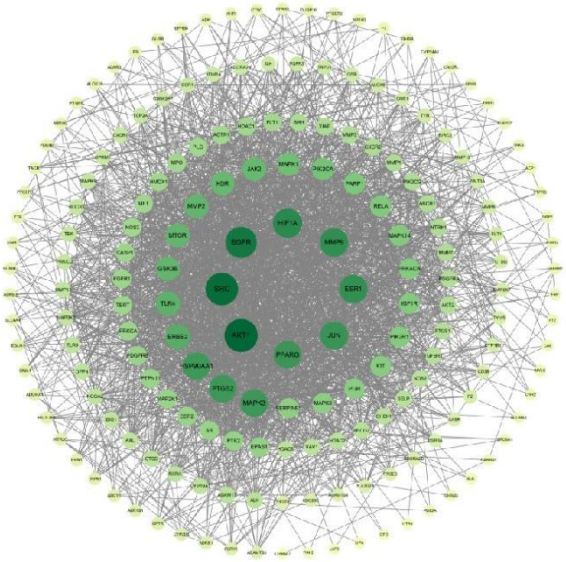

Fig. 2 PPI network diagram of potential targets for anti-periodontitis in Eucommia ulmoides

3.4 GO biological function analysis and KEGG pathway analysis

GO enrichment analysis yielded a total of 928 entries, including 700 biological process (BP), 88 cellular component (CC) and 140 molecular function (MF) entries, and the top 10 entries were selected for visualisation (Fig. 3).

The KEGG pathway enrichment analysis enriched and screened a total of 164 relevant pathways, and the top 20 pathways were selected to draw relevant bubble maps (Fig. 4).

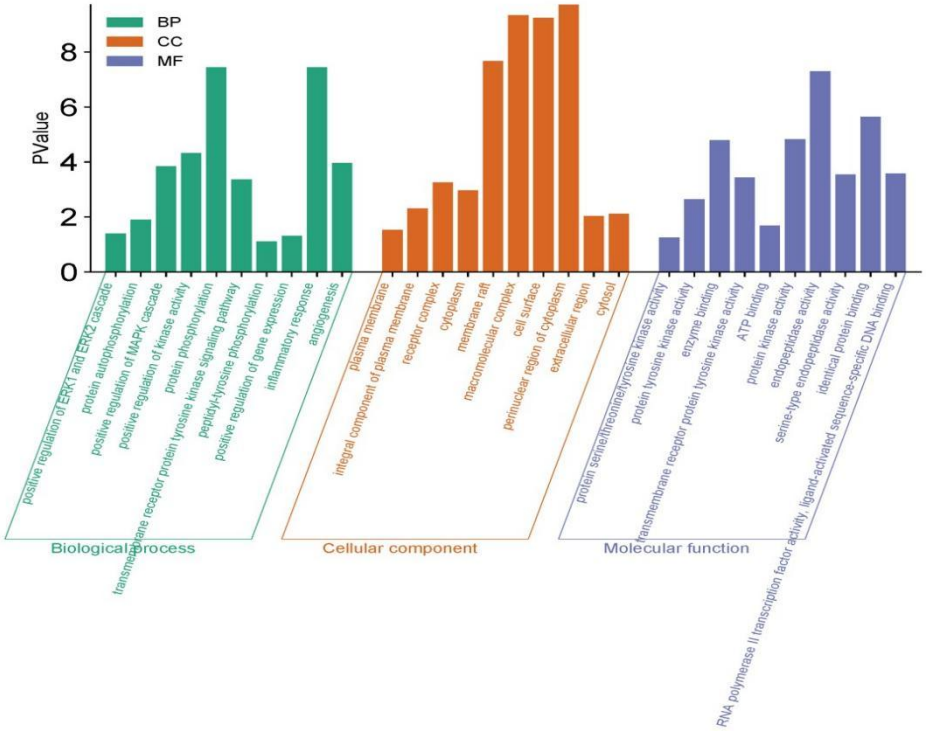

Fig. 3 GO enrichment analysis

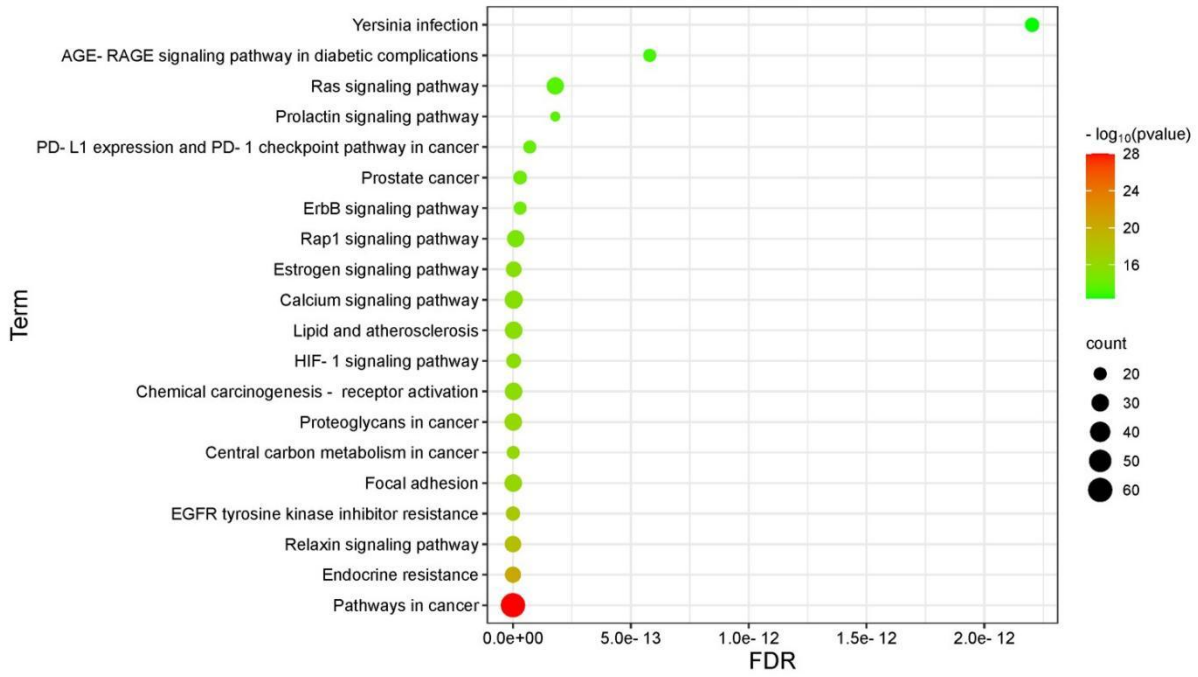

Fig. 4 KEGG pathway enrichment analysis (top 20)

KEGG enrichment analyses showed that Eucommia ulmoides was involved in the regulation of a variety of signa pathways, including the focal adhesion EGFR tyrosine kinase inhibitor resistance pathway, the relaxin signalling pathway, the hypoxia-inducible factor-1 (HIF-1) signal pathway and prolactin signaling pathway, etc[5]. It is worth noting that the prolactin signaling pathway may be associated with periodontitis, as prolactin has a regulatory effect on the immune system. In addition, HIF-1 signaling pathway may play a role in periodontitis, as there may be insufficient oxygen supply in the affected area of periodontitis[6].

4. Conclusion

The potential targets and mechanisms of action of Eucommia ulmoides through network pharmacology were analyzed in this study. The results indicate that Eucommia ulmoides exerted its therapeutic effect on periodontitis through a synergistic mechanism of multiple components, targets, and pathways. Prolactin and HIF-1 signaling pathway were noteworthy mechanism of action among them. The top 8 therapeutic targets were identified, including EGFR, HIF1A, MMP9, ESR1, JUN, PPARG, AKT1, and SRC. This study lays a theoretical foundation for the use of Eucommia ulmoides in the treatment of periodontitis and provides a stronger scientific basis for subsequent studies.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 82260767).

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