Bioinformatics-Based Investigation of the Therapeutic Mechanism and Material Basis of Eucommia ulmoides Leaves for Epilepsy Treatment

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Abstract

Objective: To investigate the mechanism of action and material basis of Eucommia ulmoides leaves in the treatment of epilepsy using bioinformatics techniques.

Methods: LC-MS technology was employed to identify the components of Eucommia ulmoides leaves, and the SuperPred database and GeneCards database were utilized to acquire component and disease targets; Cytoscape software was used to construct a network diagram; the Metascape database was applied for enrichment analysis; and CB-dock software was employed for molecular docking.

Results: A total of 113 active components and 531 targets of Eucommia ulmoides leaves, 29,880 epilepsy disease targets, 57 intersecting targets, and 9 core targets were screened; the main signaling pathways involved include cancer pathways, 5-hydroxytryptamine synapse, and other related pathways.

Conclusion: The mechanism of Eucommia ulmoides leaves in treating epilepsy may be associated with the inflammatory response, providing a scientific theoretical basis for further pharmacological studies.

Full Text

Exploring the Mechanism and Material Basis of Eucommiae Folium in Treating Epilepsy Through Bioinformatics Analysis

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Abstract

[**Objective**] To investigate the mechanism and material basis of Eucommiae Folium in treating epilepsy based on bioinformatics technology. [**Methods**] LC-MS technology was employed to identify the chemical constituents of Eucommiae Folium, and SuperPred and GeneCards databases were used to obtain component and disease targets. Cytoscape software was utilized to construct network diagrams, Metascape database for enrichment analysis, and CB-dock software for molecular docking. **Results** A total of 113 active components and 531 targets were screened from Eucommiae Folium, along with 29,880 epilepsy disease targets, yielding 57 intersection targets and 9 core targets. The main signaling pathways involved include cancer pathways and serotonin synapse pathways. [**Conclusion**] The therapeutic mechanism of Eucommiae Folium against epilepsy may be related to inflammatory responses, providing a scientific theoretical basis for further pharmacological experiments.

Keywords: Eucommiae Folium; Epilepsy; Bioinformatics; Molecular docking; Mechanism of action; Material basis

Introduction

Epilepsy is a chronic neurological disorder caused by abnormal discharge of central neurons, ranking as the second most common neurological disease in China after headache [1]. Globally, approximately 70 million people suffer from epilepsy, with a prevalence of about 5%, and mortality rates among epilepsy patients are significantly 2-3 times higher than in the general population [2, 3]. In China, an average of 400,000 new cases emerge annually [4]. Epileptic seizures are characterized by unpredictability and recurrence [5, 6]. Due to the complex etiology and pathogenesis of epilepsy, there remains no definitive cure. Current treatment primarily relies on oral antiepileptic drugs to control clinical seizures, yet a substantial portion of patients fail to achieve adequate control, resulting in high mortality rates.

In recent years, numerous clinical reports have confirmed that traditional Chinese medicine (TCM) demonstrates good efficacy in controlling epileptic seizures and improving associated symptoms [7]. TCM approaches epilepsy through understanding its etiology and pathogenesis, with rich experience showing significant therapeutic effects from both classical prescriptions and modern formulations [8, 9], offering advantages such as minimal side effects, multi-target action, and reduced epileptic complications [10]. In TCM, epilepsy falls under the category of "xian disease," with earliest records traceable to the *Huangdi Neijing*. TCM considers epilepsy a seizure disorder primarily involving abnormal consciousness, manifested by sudden fainting, tonic convulsions, and temporary recovery [11]. Shi et al. [12] propose that within the TCM theoretical framework, the core pathogenesis of epilepsy lies in the reversal and disorder

of phlegm and qi, where smooth liver qi circulation is essential for maintaining normal spleen-stomach and mental functions.

Eucommiae Folium (EF) was first included in the Chinese Pharmacopoeia in 2005 [13]. According to the 2020 edition of the Chinese Pharmacopoeia, Eucommiae Folium is the dried leaf of *Eucommia ulmoides* Oliv., possessing functions of tonifying liver and kidney, strengthening bones and muscles, and treating dizziness, soreness of waist and knees, and flaccidity of bones and muscles due to liver-kidney deficiency [13]. Modern pharmacological studies have demonstrated that Eucommiae Folium exhibits anti-inflammatory, antioxidant, and neuroprotective effects [14-16]. Eucommiae Folium extract demonstrates good neuroprotective activity and potential for treating neurodegenerative diseases [17]. Research has found that Eucommiae Folium contains the same components as *Eucommia ulmoides* bark, albeit in different proportions [18]; for instance, phenolic substances primarily exist in the leaves, and these phenolic components play important roles in explaining the antioxidant capacity of Eucommiae Folium [19]. Compounds extracted from Eucommiae Folium can inhibit the production of inflammatory factors and exert anti-neuroinflammatory effects [20].

Network pharmacology and molecular docking are emerging disciplines based on bioinformatics that employ integrated data, differential analysis, and multi-pathway, multi-target approaches to explore drug mechanisms at the molecular level, providing theoretical references for new drug development and safe medication use [21]. Since the pathogenesis of epilepsy remains unclear, this study utilizes network pharmacology, bioinformatics, and molecular docking methods to investigate the mechanism of Eucommiae Folium in treating epilepsy at the molecular and protein level, offering ideas and theoretical foundations for subsequent experimental research.

Materials and Methods

1.1 Screening of Eucommiae Folium Components and Acquisition of Predicted Targets

Chemical constituents were obtained through LC-MS technology. Following chemical component identification, the PubChem database (https://pubchem.ncbi.nlm.nih.gov) was used to obtain the SMILES number for each component. These SMILES numbers were then input into the SuperPred database (https://www.rcsb.org/) to predict chemical component targets. Predicted UniProt IDs with 98% confidence and known component IDs were merged and deduplicated. Finally, the UniProt database (https://www.uniprot.org/) was used to consolidate the data and obtain standardized target protein names.

1.2 Acquisition of Epilepsy-Related Disease Targets

The GeneCards database (https://www.genecards.org), OMIM database (https://omim.org), CTD database (http://ctdbase.org/), and TTD database

(http://db.idrblab.net/ttd/) were searched using "epilepsy" as the keyword to retrieve relevant disease targets. The data were imported into Excel, and after intersecting and removing duplicate targets, epilepsy disease targets were obtained. Using "human" as the primary filter condition, protein names of the obtained epilepsy disease targets were converted to gene names through the UniProt database.

1.3 Construction of Protein-Protein Interaction (PPI) Network for Core Genes

Disease-related targets and drug-corresponding common genes were imported into the Venny 2.1 online tool to draw Venn diagrams and obtain common target genes. These gene names were input into the STRING database (https://string-db.org/cgi/input.put.l) and searched using "multiple proteins" and *Homo sapiens*. The minimum interaction threshold was set to "medium confidence > 0.4" with free-floating nodes hidden, and other settings remained default to obtain the PPI network. The tsv format file of protein-protein interactions was downloaded from the STRING database.

1.4 Construction of Disease-Drug-Active Component-Intersection Target Network Model

Intersection targets were imported into the STRING database to construct a protein-protein interaction network. The PPI network was then imported into Cytoscape software to screen core targets, while simultaneously constructing a "drug-active component-target-disease" interaction network. The CytoNCA plugin was used to analyze topological parameters for screening major active components.

1.5 Gene Ontology (GO) Enrichment Analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway Enrichment Analysis

The Metascape platform (http://metascape.prg/gp/index.html) offers comprehensive annotation functions with monthly updated gene annotation data. Intersection targets were input into this database for GO and KEGG analysis to obtain biological processes, cellular components, molecular functions, and related signaling pathway relationships for Eucommiae Folium in treating epilepsy. Data files were downloaded and visualized on the Bioinformatics website (http://www.bioinformatics.com.cn/).

1.6 Molecular Docking

SDF structure files of compounds were retrieved through the PubChem website, and PDB structure files of receptors were obtained through the UniProt database. The CB-dock website was then used to set the cavity number to 5 and perform molecular docking.

Results

2.1 Screening of Eucommiae Folium Chemical Components

A total of 113 components were obtained through LC-MS technology. Based on the SuperPred database, targets for these 113 active components were collected. After selecting 98% confidence predictions and known IDs and removing duplicates, 60 component targets were obtained.

2.2 Epilepsy Disease-Related Targets

From the GeneCards database, 778 epilepsy target entries were obtained; from CTD, 29,880 entries; from OMIM, 645 entries; and from TTD, 34 entries. After merging the four databases and using CTD as the standard, duplicate genes were removed using Excel, yielding 29,880 related gene entries. Venn diagrams were used to obtain intersection targets between components and diseases, as shown in [Figure 1: see original paper].

[Figure 1: see original paper] Drug-Disease Venn Analysis Diagram

2.3 Construction of Eucommiae Folium Active Component-Target-Drug-Disease Network and PPI Analysis

Using the CytoNCA plugin, five main active components of Eucommiae Folium for treating epilepsy were screened: quercetin, myricetin, kaempferol, isoquercitrin, and hyperoside. The network diagram consisted of 122 nodes and 310 edges, as shown in [Figure 2: see original paper].

The core network was screened based on average and maximum degrees, as shown in [Figure 3: see original paper]. The core genes were ranked by degree: tumor necrosis factor (24), proto-oncogene tyrosine-protein kinase Src (21), hypoxia-inducible factor (21), prostaglandin synthase 2 (21), matrix metalloproteinase 9 (17), serine/threonine protein kinase (17), vascular endothelial growth factor (16), mitogen-activated protein kinase 1 (16), and hepatocyte growth factor receptor (13).

[Figure 2: see original paper] "Disease-Target-Component-Drug" Network Diagram of Eucommiae Folium in Treating Epilepsy
[Figure 3: see original paper] Protein-Protein Interaction Network Diagram (plotted according to degree value; larger degree values correspond to larger target areas)

2.4 Enrichment Analysis Results

GO and KEGG analyses were performed using the Metascape database, with P-value < 0.01 as the screening criterion. A total of 597 BP entries, 43 CC entries, and 44 MF entries were obtained. The top ten were selected for analysis based on FDR values, as shown in [Figure 4: see original paper]. KEGG analysis

yielded 91 pathways, with the top ten selected for analysis, as shown in [Figure 5: see original paper].

[Figure 4: see original paper] GO Enrichment Analysis
[Figure 5: see original paper] KEGG Pathway Enrichment Analysis Bubble Chart (x-axis represents FDR, y-axis represents Term, color indicates P-value, and point size represents count)

2.5 Molecular Docking Results

Molecular docking of active components and targets is shown in . Among 45 molecular docking relationships, the binding energies between important targets and effective components are presented, all of which were ≤ -5 kJ/mol, indicating stable binding between targets and components. This study selected five components (quercetin, myricetin, kaempferol, isoquercitrin, hyperoside) and their binding degrees with nine genes (TNF, HIF1A, PTGS2, MMP9, SRC, MTOR, KDR, MAPK1, MET).

Molecular Docking Results

Discussion

The rise of bioinformatics stems from recent advances in comprehensive biological information analysis, offering potential for innovative therapeutic options [22]. This study aimed to identify key genes and components of Eucommiae Folium in treating epilepsy and explain potential mechanisms through bioinformatics analysis.

This study screened five core components and nine core targets of Eucommiae Folium, involving 91 main pathways and 684 biological processes. The "disease-target-component-drug" network revealed that the main components of Eucommiae Folium—quercetin, myricetin, kaempferol, isoquercitrin, and hyperoside—can synergistically act on multiple targets. Quercetin is a plant-derived flavonoid with various pharmacological activities, and emerging evidence demonstrates its antiepileptic effects [23]. Studies show quercetin possesses anti-inflammatory, anti-infective, and neuroprotective properties [24]. Previous research found that quercetin exhibits therapeutic effects against epilepsy, primarily by improving oxidative damage and downregulating inflammatory responses [25, 26]. In a kainic acid (KA) (10 mg/kg)-induced model of epileptic seizures in BALB/c mice, quercetin treatment significantly reduced KA-induced seizure activity, with lower seizure scores compared to the KA treatment group. Myricetin is structurally similar to quercetin and reportedly shares many functions with other flavanol flavonoids [27], exhibiting various biological activities including antioxidant [28], protection against nervous system damage [29], antiepileptic [30], and anti-inflammatory effects [31]. Kaempferol is a polyphenol widely found in fruits, vegetables, and herbs, with studies demonstrating its anti-inflammatory effects [32]. Isoquercitrin possesses antioxidant and anti-inflammatory activities and is considered a

neuroprotective agent [33, 34]. Hyperoside protects hippocampal CA3 regions from epilepsy-induced neuronal damage by enhancing antioxidant levels and reducing autophagy [35].

Furthermore, we analyzed nine core targets acting on the organism: TNF, SRC, MTOR, KDR, HIF1A, MET, MMP9, PTGS2, and MAPK1. TNF is an inflammatory factor, and epileptic seizures are accompanied by increased tumor necrosis factor α (TNFα) [36]. Overexpression of inflammatory factors can increase glutamate release, leading to hippocampal sclerosis and inducing epilepsy. Dysregulation of SRC family kinases contributes to epileptogenesis, and SRC activation in epilepsy may be caused by inflammatory responses and participates in seizure development [37, 38]. MTOR signal activation is associated with inflammatory responses in epileptic states; when seizures occur, MTOR upregulation triggers epilepsy [39]. KDR, also known as VEGFR-2, is activated during epileptic seizures. Angiogenesis is associated with increased blood-brain barrier permeability through vascular endothelial growth factor-induced inflammation, affecting local vascular networks, triggering neuroinflammatory factors, and promoting atrophy and seizure progression [40]. Studies show that HIF-1α causes TNF-α upregulation, and inhibiting HIF-1α significantly attenuates amplified TNF-α in these brain regions. During epileptogenesis, enhanced HIF-1α activity in specific brain regions promotes neuronal damage through TNF-α mechanisms [41]. Small molecule inhibitors (Inh) of Met can block inflammatory signal transduction and limit microglial aggregation. Met activation may induce reactive phenotypes and lead to inflammatory cytokine induction [42]. MMP-9 participates in epileptic focus formation and activation of post-seizure inflammatory processes by altering the blood-brain barrier and cell death [43]. PTGS2 is an important pro-inflammatory mediator strongly activated during inflammation, and elevated levels of pro-inflammatory mediators (TNF-α, PTGS2) are considered to be caused by central spreading of extracellular diffusion pathways involving NF-kB activation in epilepsy [44]. MAPK1, also known as P38 or ERK, is an inflammatory mediator that upregulates during seizures and causes epileptic episodes [45]. ERK inhibitors reduce seizure-induced ERK and p38 activation and significantly decrease the protective effect of initial seizures on CA3 neurons [46].

In summary, bioinformatics can be used to analyze the mechanism and material basis of Eucommiae Folium in treating epilepsy. Multiple chemical components in Eucommiae Folium primarily affect the inflammatory process of epilepsy to exert therapeutic effects.

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Note: Figure translations are in progress. See original paper for figures.