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Exploring the Pharmacological Mechanism of Asari Radix Et Rhizoma against Trigeminal Neuralgia: A Network Pharmacology and Molecular Docking Approach

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Abstract

Background: Asari Radix Et Rhizoma is extensively used to treat trigeminal neuralgia in China. However, the underlying mechanism of Asari Radix Et Rhizoma in the treatment of trigeminal neuralgia is unknown.

Objective: Investigate the possible pharmacological mechanism of Asari Radix Et Rhizoma in the treatment of trigeminal neuralgia using network pharmacology and molecular docking.

Methods: The TCMSP database was used to retrieve the active components of Asari Radix Et Rhizoma. The essential components of Asari Radix Et Rhizoma were obtained by drawing an active component-target network diagram with Cytoscape software. The corresponding targets were then obtained from the TCMSP database. The GeneCards, DisGeNET, and OMIM databases were searched for targets associated with trigeminal neuralgia. The String database was used to create a PPI network of common pharmaceutical and ailment targets before obtaining the core targets. The David database was used for common target GO enrichment and KEGG pathway analysis. After that, AutoDock performed molecular docking between the critical component and the critical target.

Results: According to a review of the literature, the key components of Asari Radix Et Rhizoma in the treatment of trigeminal neuralgia are kaempferol, Cryptopin, and Sesamin, which may act on key targets like AKT1, JUN, ESR1, TNF, and MAPK8. KEGG enrichment analysis revealed the following key pathways: Lipid and atherosclerosis, Fluid shear stress and atherosclerosis, AGE-RAGE signaling route in diabetic complications, TNF signaling pathway, Estrogen signaling pathway, and so on. However further research is needed to establish the specific mechanism of Asari Radix Et Rhizoma. The affinity between the core components and core components was shown by molecular docking studies.

Conclusion: The article provided a preliminary explanation of the possible mechanism of Asari Radix Et Rhizoma in the treatment of trigeminal neuralgia, which can serve as a theoretical foundation and evidence for further experimental research.

Keywords: Asari Radix Et Rhizoma; Trigeminal neuralgia; Network pharmacology; Molecular docking

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Abbreviations

ADME: Adsorption, Distribution, Metabolism, Excretion; AGE-RAGE: Advanced Glycation End, product-Receptor for AGE; AGEs: Advanced Glycation End products; AKT1: Serine/Threonine Kinase 1; Asari Radix: Asari Radix et Rhizoma; BP: Biological Processes; CC: Closeness Centrality; CTN: Classical TN; DL: Drug-Likeness; DNA: Deoxyribonucleic Acid; ESR1: Estrogen Receptor 1; GABA: Gamma-Aminobutyric Acid; GO: Gene Ontology; GT1b: Genotype 1b; HO-1: Heme Oxygenase-1; IL-1β: Interleukin-1β; i.t: Intrathecal; JUN: Transcription Factor AP-1; KEGG: Kyoto Encyclopedia of Genes and Genomes; MAPK 8: Mitogen-Activated Protein Kinase 8; Nrf 2: NF-E2 p45-related factor 2; OB: Oral Bioavailability; PGC 1α: Proliferator-Activated Receptor-Gamma Coactivator -1α; PI3K/AKT: Phosphoinositide 3-Kinase- Protein Kinase B; PPI: Protein–Protein Interaction; RNA: Ribonucleic Acid; SIRT 1: Sirtuin 1; STN: Secondary TN; TCMSP: Traditional Chinese Medicine Systems Pharmacology database and analysis Platform; TN: Trigeminal Neuralgia; TNF: Tumor Necrosis Factor; TNF-α: Tumor Necrosis Factor-α

Introduction

Touch-evoked unilateral short shock-like paroxysmal pain in one or more trigeminal nerve divisions is the hallmark of Trigeminal Neuralgia (TN). Some patients experience persistent pain in addition to paroxysmal pain. There are two types of TN: Secondary TN (STN) and Classical TN (CTN). TN is often underdiagnosed as well as misdiagnosed. Studies have found varying incidences of TN, ranging from 4.3 to 27 new cases per 100,000 individuals per year [1-3]. Women experience a greater incidence rate, which rises with age [1]. Based on population-based studies, the lifetime prevalence was estimated to be 0.16% to 0.3% [2,4].

Trigeminal Neuralgia (TN) is characterized by touch-evoked unilateral brief shock-like paroxysmal pain in one or more divisions of the trigeminal nerve. In addition to the paroxysmal pain, some patients also have continuous pain. TN is divided into Classical TN (CTN) and Secondary TN (STN). TN is frequently both misdiagnosed and underdiagnosed. The incidence of TN is variably reported between studies, with a range from 4.3 to 27 new cases per 100,000 people per year [1-3]. The incidence is higher among women and increases with age [1]. The lifetime prevalence was estimated to be 0.16% to 0.3% in population-based studies [2,4]. Although the age of onset can vary from early infancy to old age, it typically occurs in secondary TN at around 43 years old and in classical TN at 53 years old [5,6]. STN accounted for 14% to 20% of TN patients in studies based on tertiary care [5,7]. Compression of the blood vessels, primarily in the arteries, or other morphological alterations are currently the most common causes of TN. This is known as the compression and neurovascular conflict. To develop new therapeutic approaches, it is imperative to comprehend the molecular etiology of trigeminal neuralgia, as the precise mechanism of action of this condition is yet unknown.

In Chinese medicine therapy, Asari Radix et Rhizoma (Asari Radix) is one of the most often prescribed medicines [8]. Since ancient times, it has been commonly used to treat trigeminal neuralgia, colds, headaches, coughs, and toothaches. Its use was originally documented in the Shennong's Classic of Materia Medica, or Shennong Bencaojing in Chinese [9-12]. Nevertheless, it is unclear what fundamental mechanisms underlie their trigeminal neuralgia diagnosis and treatment.

Based on systems biology theory, network pharmacology is an emerging multidisciplinary area that combines bioinformatics and computer science. The "multi-component, separate-target, multi-pathway" synergistic interaction between medications, illnesses, and targets can be examined using network pharmacology. Understanding the pharmacological mechanism of traditional Chinese medicine, investigating the toxicological mechanism of traditional Chinese medicine, and investigating and developing novel traditional Chinese medicine have all benefited much from it. Molecular docking makes use of known-structured receptors and ligands to identify molecular interactions and predict the best molecular binding mode by combining the complementary ideas of geometry, energy, and chemical environment. It provides substantial value and potential advantages for studying the pharmacological mechanism of Chinese

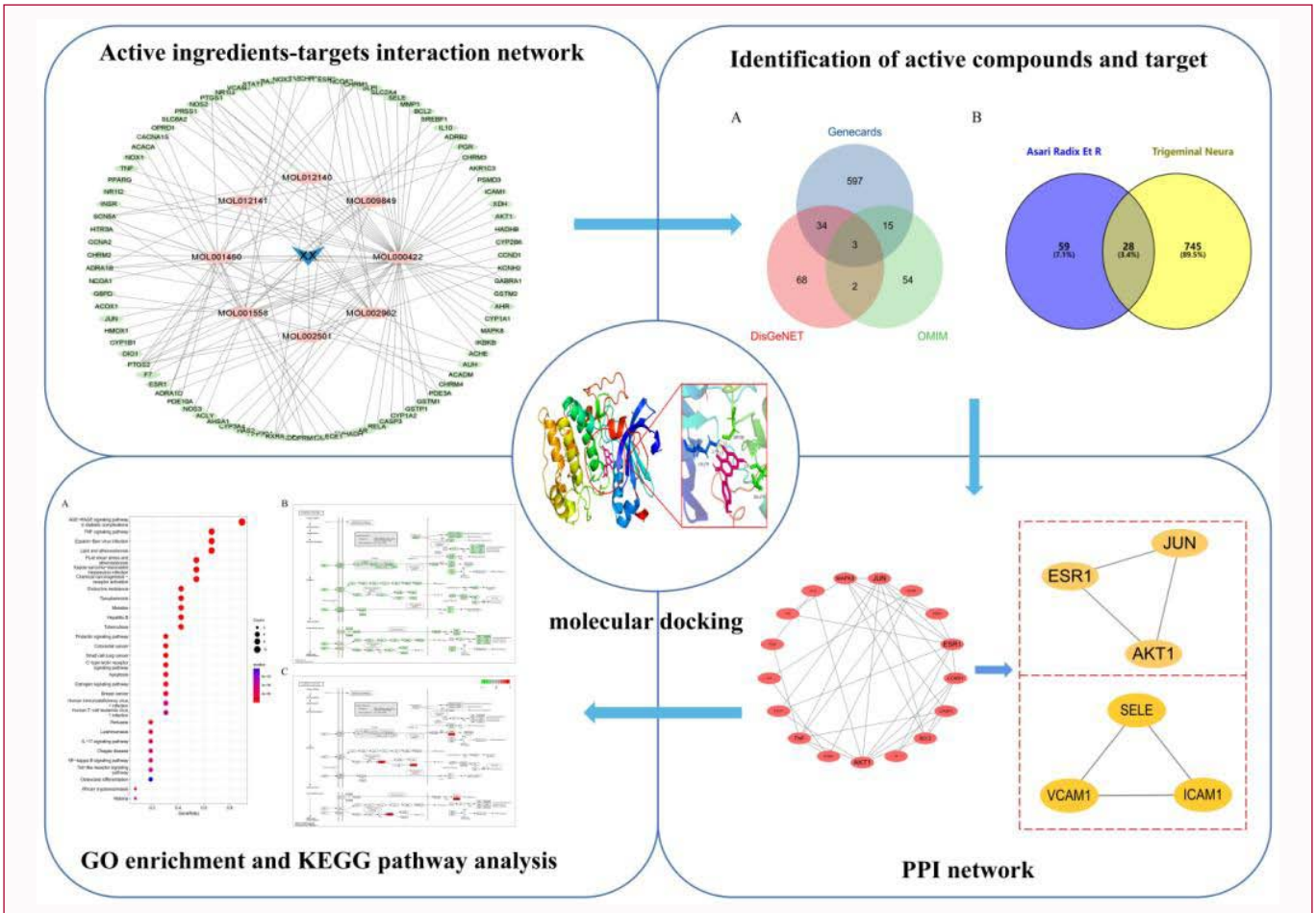

Figure 1: Graphical abstract.

herbal compound prescriptions as well as the potential target and mode of action of active ingredients in traditional Chinese medicine. This study aims to analyze the likely mechanism of Asari Radix et Rhizoma in the treatment of trigeminal neuralgia using molecular docking and traditional Chinese medicine network pharmacology to provide a theoretical framework for future research. The following is how the graphical abstract appeared (Figure 1).

Materials and Methods

Materials

Databases: Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, https://tcmspw.com/index.php) [13], UniProt database (http://www.uniprot.org) [14], GeneCards database (https://www.genecards.org), DisGeNET database (https://www.disgenet.org), OMIM database (https://omim.org) [15] String database (Version 11.0, https://string-db.org) [16], DAVID database (https://david.ncifcrf.gov) [17], PDB database (https://www.rcsb.org).

Online drawing tools: Venny (Version 2.1.0, https://bioinfogp.cnb.csic.es/tools/venny), Bioinformatics (http://www.bioinformatics.com.cn).

Software: Cytoscape software (version 3.8), AutoDock software (version 4.2.6), AutoDock Tools software (version 1.5.6), PyMOL software (version 2.4.0).

Screening of compositions and targets in Asari Radix Et Rhizoma

The TCMSP database was used to gather the chemical compositions of Asari Radix Et Rhizoma. The active components were then evaluated based on Adsorption, Distribution, Metabolism, and Excretion (ADME), satisfying the two requirements of Oral Bioavailability (OB) ≥ 30% and Drug-Like (DL) ≥ 0.18. Following the acquisition of each drug's active components, the matching targets were also looked up in the TCMSP database, and the UniProt database standardized the target name. The Asari Radix Et Rhizoma active components-targets network diagram was created using Cytoscape software, and the network analyzer feature of the program was utilized to perform the topological study. Asari Radix Et Rhizoma's essential elements were derived based on the degree value.

Screening of trigeminal neuralgia-related targets

With 'trigeminal neuralgia' (Mesh) as the primary search term, targets associated with the condition were obtained from the GeneCards, DisGeNET, and OMIM databases. The trigeminal neuralgia-related targets were obtained by combining the targets that were retrieved from the aforementioned database and eliminating duplicates.

Construction of a Protein–Protein Interaction (PPI) network between interaction targets and acquisition of core targets

Venny was used to identify the interaction targets between Asari Radix Et Rhizoma and trigeminal neuralgia, after which a Venn diagram was created. The String database was used to create the PPI network connecting the interaction targets. The organism was Homo sapiens, and the mechanism was "Multiple Protein." "Highest confidence (0.900)" was the lowest required interaction score, and the network's unconnected nodes were buried. The other settings did not change. For visual analysis, the acquired node1, node2, and total score were loaded into the Cytoscape program. The software's network analyzer capability was utilized for topological analysis, and the degree value was used to determine the main targets of Asari Radix Et Rhizoma in the treatment of trigeminal neuralgia.

GO enrichment and KEGG pathway analysis

Using the DAVID database, Gene Ontology (GO) enrichment and KEGG pathway analysis were carried out on the interaction targets of trigeminal neuralgia and Asari Radix Et Rhizoma. The background and species were both set to "Homo sapiens," while the select identifier was set to "OFFICIAL GENE SYMBOL." Next, analyses of the KEGG pathway, Molecular Function (MF), Cell Component (CC), and Biological Process (BP) were carried out. After being exported, the data was sorted by P value. Bioinformatics chose the ten items with the lowest P-value for each GO enrichment to create a bar chart and 20 items with the lowest P-value for each KEGG pathway were chosen by Bioinformatics to create the advanced bubble diagram.

Construction of targets-pathways interaction network

The Cytoscape software was utilized to import the 20 items that had the lowest P-value in the KEGG pathways. Additionally, the software was used to import the interaction targets between the compounds and disease targets that were part of the KEGG pathways mentioned above. Afterward, an interaction network between the targets and pathways was created.

Results

Obtainment of components and targets in Asari Radix Et Rhizoma

The TCMSP database provided the targets and components for Asari Radix Et Rhizoma, with OB >30% and DL ≥ 0.18 serving as the inclusion criteria. Eight active components were found after the non-target components and duplication were removed. All 8 active components were displayed in Table 1 and were ordered from large to small based on the OB value. A total of 87 targets of Asari Radix Et Rhizoma were searched by obtaining the TCMSP database. Target names were standardized using the UniProt database, and repetitive values were eliminated. The Asari Radix Et Rhizoma active components-targets interaction network was drawn using Cytoscape software (Figure 2). The top three core components of Asari Radix Et Rhizoma were kaempferol, Cryptopin, and Sesamin according to the degree value of the network analyzer function of the software.

Acquisition of trigeminal neuralgia-related targets

A total of 649 trigeminal neuralgia-related targets were found in the GeneCards database, 107 in the DisGeNET database, and 74 in the OMIM database (Figure 3A). These results were accumulated from three different sources. In the end, 773 targets linked to trigeminal neuralgia were obtained after the targets from the three databases were combined and the duplicate values were removed.

Construction of a Protein–Protein Interaction (PPI) network between interaction targets and acquisition of core targets

Venny was used to obtain trigeminal neuralgia and 28 Asari Radix Et Rhizoma interaction targets (Figure 3B). Building PPI networks by importing 28 interaction targets into the String database (the disconnected nodes in the network were hidden). For visual analysis, the acquired node1, node2, and total score were loaded into the Cytoscape program (Figure 4A). Topological analysis was conducted using the software's network analyzer tool. The primary targets of Asari Radix Et Rhizoma in the therapy of trigeminal neuralgia were

Table 1: Active components of Asari Radix et Rhizoma.

Mol ID	Molecule Name	OB (%)	DL (%)
MOL001460	Cryptopin	78.74	0.72
MOL012140	4,9-dimethoxy-1-vinyl-$b-carboline	65.3	0.19
MOL002501	[(1S)-3-[(E)-but-2-enyl]-2-methyl-4-oxo-1-cyclopent-2-enyl] (1R,3R)-3-[(E)-3-methoxy-2-methyl-3-oxoprop-1-enyl]-2,2-dimethylcyclopropane-1-carboxylate	62.52	0.31
MOL001558	Sesamin	56.55	0.83
MOL002962	(3S)-7-hydroxy-3-(2,3,4-trimethoxyphenyl)chroman-4-one	48.23	0.33
MOL000422	kaempferol	41.88	0.24
MOL012141	Caribine	37.06	0.83
MOL009849	ZINC05223929	31.57	0.83

Table 2: The binding energy results.

Compounds	Target	PDB ID	Center (X, Y, Z)	Binding free energy (kcal/mol)
Kaempferol	AKT1	6CCY	(-9.801, 15.312, -31.398)	-5.9
	JUN	5FV8	(34.364, 3.119, -3.095)	-4.05
Cryptopin	AKT1	6CCY	(-9.801, 15.312, -31.398)	-7.12
	JUN	5FV8	(34.364, 3.119, -3.095)	-4.79
Sesamin	AKT1	6CCY	(-9.801, 15.312, -31.398)	-7.19
	JUN	5FV8	(34.364, 3.119, -3.095)	-5.58

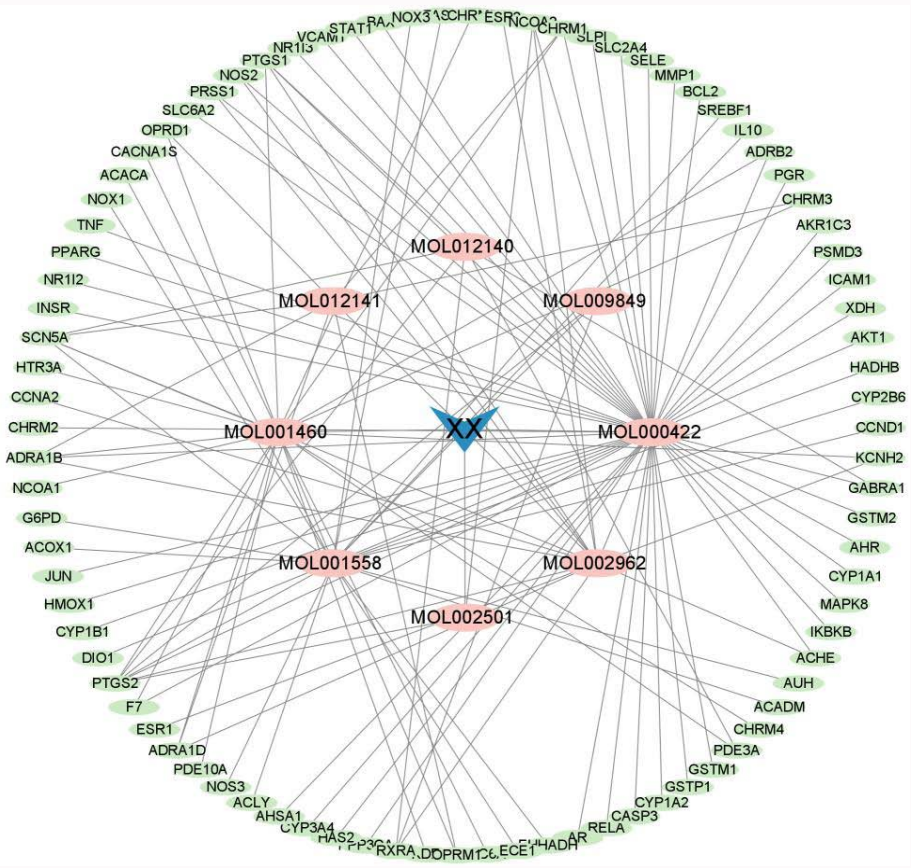

Figure 2: Active components-targets interaction network of Asari Radix Et Rhizoma.

AKT1, JUN and ESR1, or SELE, VCAM1and ICAM1 based on the degree value (Figure 4B).

GO enrichment and KEGG pathway analysis

For GO enrichment and KEGG pathway analysis, the 28 interaction targets between trigeminal neuralgia and Asari Radix Et Rhizoma were imported into the Metascape database. There were 155 Biological Processes (BP), 27 Cellular Components (CC), 45 Molecular Functions (MF), and 92 KEGG pathways found. After being exported, the data was sorted by P value. Bioinformatics chose

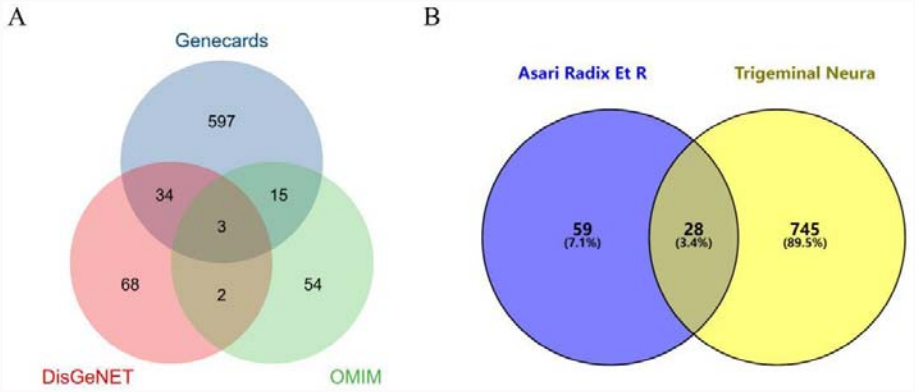

Figure 3: (A) The Venn diagram of Asari Radix Et Rhizoma was constructed by GeneCards, DisGeNET and OMIM databases. (B) Venn diagram of interaction targets of Asari Radix Et Rhizoma and trigeminal neuralgia.

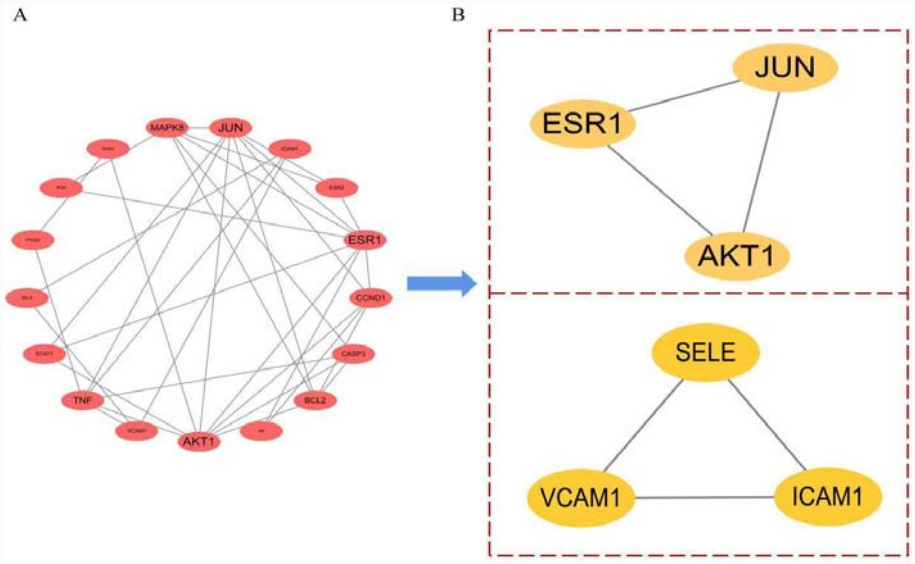

Figure 4: PPI network construction of core target.

the ten items with the lowest P-value for each GO enrichment to create a bar chart and the 20 items with the lowest P-value for each KEGG pathway were chosen to create the figure.

The top 10 enrichment results of GO-BP were: response to xenobiotic stimulus, positive regulation of nitric oxide biosynthetic process, intracellular steroid hormone receptor signaling pathway, response to lipopolysaccharide, positive regulation of apoptotic process, response to estradiol, positive regulation of sequence-specific Deoxyribonucleic Acid (DNA) binding transcription factor activity, signal transduction, positive regulation of transcription, DNA-templated, and positive regulation of pri-miRNA transcription from Ribonucleic Acid (RNA) polymerase II promoter. The top 10 enrichment results of GO-CC were: Membrane raft, plasma membrane, nucleoplasm, macromolecular complex, integral component of plasma membrane, synapse, neuron projection, cell surface, perinuclear region of cytoplasm, and chromatin. The top 10 enrichment results of GO-MF were: Enzyme binding, steroid binding, estrogen response element binding, RNA polymerase II transcription factor activity, ligand-activated sequence-specific DNA binding, transcription coactivator binding, sequence-specific DNA binding, transcription factor activity, sequence-specific DNA binding, protein binding, steroid hormone receptor activity, and identical protein binding (Figure 5).

The top 20 KEGG enrichment results were AGE-RAGE signaling pathway in diabetic complications, TNF signaling pathway, Lipid and atherosclerosis, Pathways in cancer, Epstein-Barr virus infection, Fluid shear stress and atherosclerosis, Chemical carcinogenesis - receptor activation, Endocrine resistance, Toxoplasmosis, Kaposi sarcoma-associated herpesvirus infection, Prolactin signaling pathway, Estrogen signaling pathway, Measles, Colorectal cancer, Hepatitis B, Small cell lung cancer, Tuberculosis, C-type lectin receptor signaling pathway, Osteoclast differentiation, Apoptosis (Figure 6A). AGE-RAGE signaling pathway in diabetic complications (Figure 6B, 6C). In addition, we constructed a target-pathway network to determine the specific pathway enrichment in which the target participated (Figure 7).

Molecular docking results

The primary targets (AKT1 and JUN) and the core components (kaempferol, Cryptopin, and Sesamin) were matched using molecular docking. Stronger affinity between the ligand and receptor is indicated by a more stable conformation, which decreases the binding free

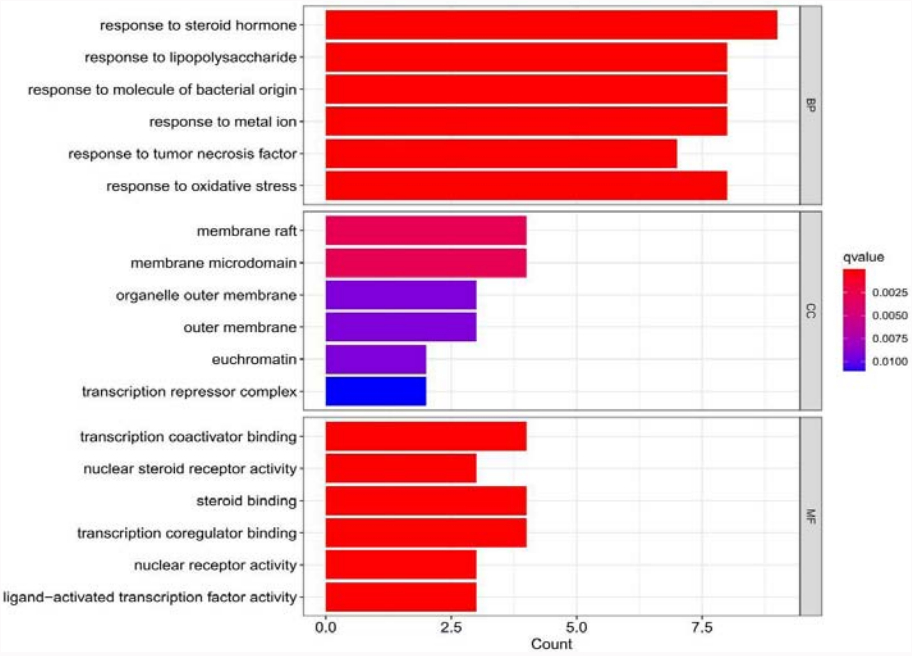

Figure 5: The top 10 enrichment results of GO-BP, GO-CC, and GO-MF.

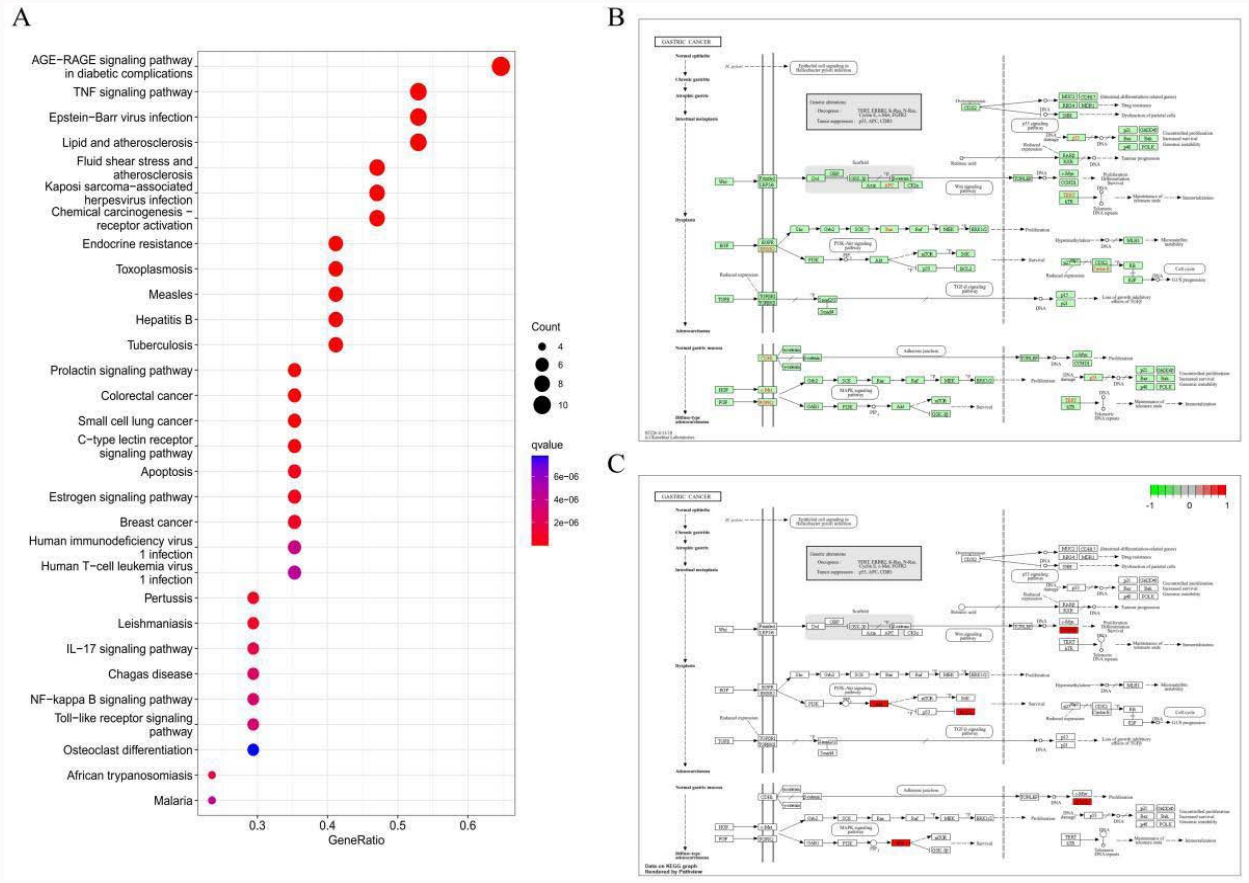

Figure 6: (A) The top 20 enrichment results of KEGG. (B, C) AGE-RAGE signaling pathway in diabetic complications.

energy between them [18]. Generally speaking, spontaneous binding between the ligand and receptor is indicated when the binding free energy is less than 0 [19]. In this work, the binding energy results from molecular docking were displayed (Table 2). PyMOL was used to show the molecular docking results (Figure 8).

Discussion

Asari Radix et Rhizoma is a plant of *Aristolochia* family of

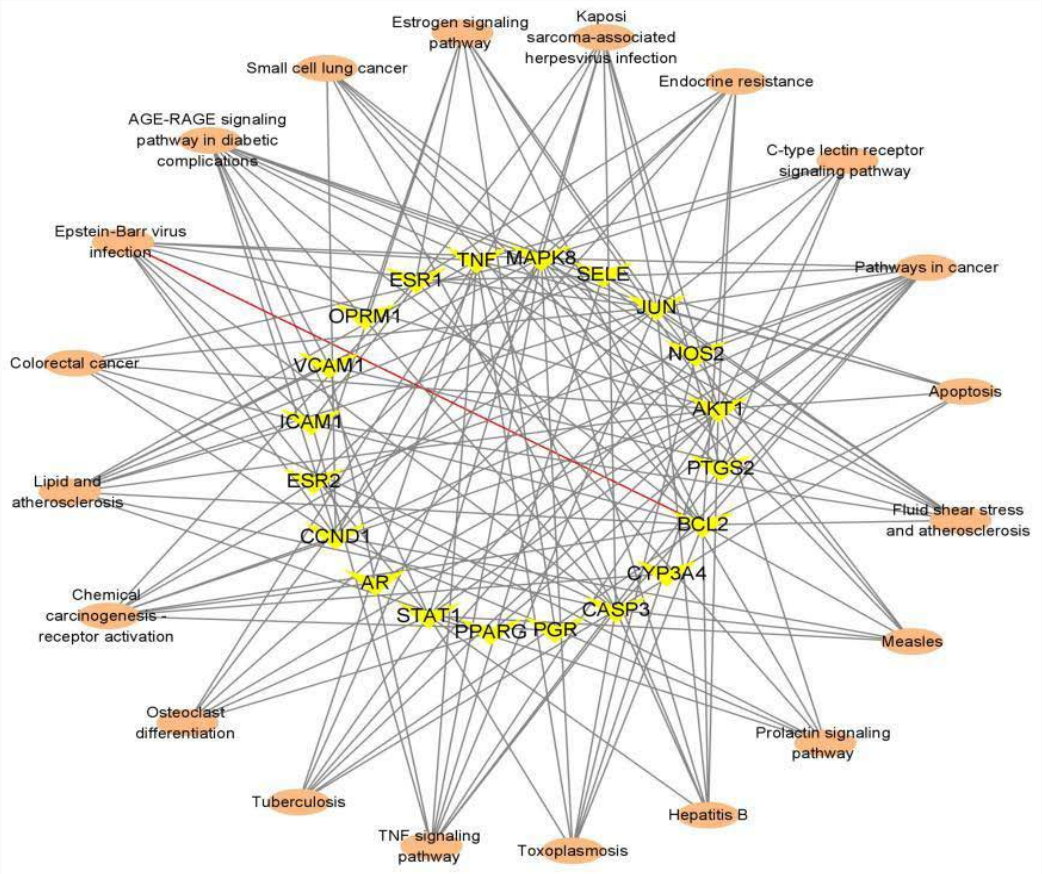

Figure 7: Targets-pathways interaction network.

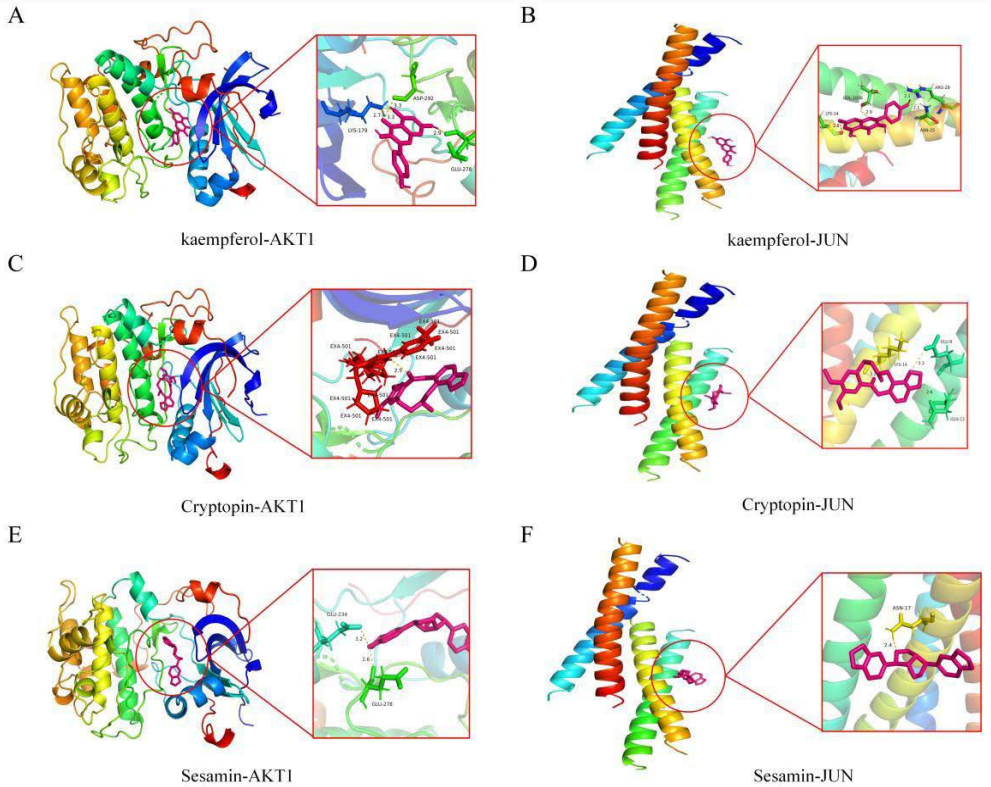

Figure 8: The molecular docking results were visualized by PyMOL.

Aristolochia order. It has the functions of dispelling cold to relieve exterior syndrome, dispelling wind to relieve pain, relieving stuffy nose and warming the lung for resolving fluid retention, and is often used in wind-cold cold, various headaches, toothaches, rheumatism and arthralgia, etc. [20,21]. Modern pharmacological studies have shown that Asari Radix et Rhizoma not only has antipyretic, analgesic, anti-inflammatory, asthmatic, immune enhancement, metabolism enhancement, antibacterial, and other effects [22].

Our investigation revealed that the primary constituents of Asari Radix et Rhizoma include kaempferol, Cryptopin, and Sesamin. which trigeminal neuralgia is closely associated with [23]. Trigeminal neuralgia is an excruciatingly painful neurological disorder characterized by intense, stimulus-evoked, transient facial stabbing pain attacks [24]. The patient's condition was assessed to look for potential neurovascular contact. To show how vascular compression has changed the morphology of the trigeminal roots, classical TN is necessary. Neurological illnesses that can be identified as underlying causes induce secondary TN [25]. According to recent research, kaempferol shields blood vessels from oxidative stress and inflammation-induced damage, and it is crucial for the NF-E2 p45-related factor 2 (Nrf 2)/Heme Oxygenase-1 (HO-1) signaling pathway to mediate these benefits [26]. According to an animal investigation, kaempferol alleviated right ventricular hypertrophy in HPH rats and decreased pulmonary artery pressure and pulmonary vascular remodeling [27]. Research has demonstrated that Cryptopin protects blood vessels and prevents cardiovascular illnesses by acting as an antioxidant [28]. Related research showed that Sesamin had neuroprotective, antiproliferative, antihypertensive, and antioxidant properties. It also showed that by controlling glutamatergic and Gamma-Aminobutyric Acid (GABA) transmission in the mouse amygdala, Sesamin at least partially attenuated anxiety-like behaviors brought on by chronic pain [29]. Additionally, some research has demonstrated that Sesamin relieves neuralgia [30].

The PPI was used to determine the primary targets of this investigation, which were AKT1, JUN, ESR1, TNF, and MAPK8. Studies that are pertinent to the matter have demonstrated that the Phosphoinositide 3-kinase-Protein Kinase B (PI3K/AKT) intracellular signaling pathway is a viable target for preventing the peripheral nervous system from developing morphine tolerance. New analgesic medication therapies will be developed as a result of ongoing study into this mechanism [31]. The suppression of paclitaxel-induced neuropathic pain is achieved by the investigators' experimental validation of the modulation of RES activating PI3K/Akt and Sirtuin 1 (SIRT 1)/Proliferator-activated receptor-Gamma Coactivator -1α (PGC 1α) pathways. AKT1 has been shown in a network pharmacology study to concurrently alleviate neuropathic pain and neuropathic inflammation [32]. According to related research, JUN may be able to protect against neurodegeneration and injury by activating neural cells [33]. TNF-α is thought to be a major proinflammatory cytokine that can drive cytokine storm and stimulate the cascade of other cytokines in pain-related pathways by promoting peripheral (primary afferents) and central (spinal cord) sensitization to induce and regulate neuropathic pain, according to a growing body of research on the neurogenic pain neuroimmune mechanism [34]. Some researchers think that elevated amounts of the inflammatory protein TNF-α cause neuropathic pain, which is a persistent pain following nerve damage. Research has demonstrated that injury to peripheral nerves raises TNF in the hippocampal/pain perception region, which in turn regulates feelings of neuropathic pain. The study targeting central TNF by perispinal drug delivery may be a more effective and durable approach for treating patients with neuropathic pain [35].

The primary pathways were identified by KEGG enrichment analysis as follows: TNF signaling pathway, estrogen signaling pathway, AGE-RAGE signaling pathway in diabetic complications, lipid and atherosclerosis, fluid shear stress and atherosclerosis, and so on. Among them, lipid and atherosclerosis are important factors in Numerous mediators produced from membrane lipids and are essential for the onset, maintenance, and control of different kinds of acute and chronic pain [36]. According to related research, atherosclerosis in the cross-compression of blood arteries is referred to as local pathogenesis, which results in several dysfunction syndromes, including hemifacial spasm and trigeminal neuralgia [37]. According to one study, 43 out of 125 patients with trigeminal neuralgia had cerebral atherosclerosis along the course of their condition. There is growing evidence that atherosclerosis and trigeminal pain are intimately associated, and that the interaction between AGEs and the RAGE receptor is a major factor in the development of atherosclerosis [38-40]. Additionally, it has been shown that estrogen increases vulnerability to cortical diffusion inhibition, a neurobiological process that occurs before migraine [41]. While estrogen exerts anti-inflammatory and neuroprotective effects on the nervous system, our study also revealed that intrathecal (i.t). Genotype 1b (GT1b) administration induces central pain sensitization in a sexually dimorphic manner. We discovered that estrogen is responsible for sexual dimorphism and that estrogen ameliorates GT1b-induced Interleukin-1β (IL-1β) production in the spinal cord by inhibiting inflammasome activation as an underlying mechanism. Our research may clarify sex-specific treatment approaches that use estrogen to address central pain sensitivity [42]. The pathway enrichment analysis indicates that the primary effects of the target genes of the effective components of trigeminal neuralgia on trigeminal pain regulation are related to vascular morphology, oxidative stress, vascular sclerosis prevention, and other related characteristics.

Conclusion

This study showed that Asari Radix Et Rhizoma treated trigeminal neuralgia through multiple compounds, multiple targets, and multiple pathways based on network pharmacological analysis. It also partially clarified the associated potential mechanism of Asari Radix Et Rhizoma in the treatment of trigeminal neuralgia. Asari Radix Et Rhizoma was discovered to have a significant impact on the treatment of trigeminal neuralgia through KEGG pathway enrichment analysis. This included the following: Lipid and atherosclerosis, Fluid shear stress and atherosclerosis, AGE-RAGE signaling pathway in diabetic complications, TNF signaling pathway, Estrogen signaling pathway, and so on. While further verifications are necessary to ascertain the precise mechanism of Asari Radix Et Rhizoma, the current investigation offers encouraging avenues for further investigation.

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