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# Explore the pharmacological basis of ShengJiYiSui decoction in the treatment of amyotrophic lateral sclerosis based on network pharmacology and molecular docking technology

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**ABSTRACT**

Neurodegenerative illnesses have long been handled clinically by traditional Chinese medicine. This study is the first time to explore the pharmacological basis of application in amyotrophic lateral sclerosis (ALS) through network pharmacology and molecular docking techniques. In the present investigation, the TCMSP database and HIT2 database were examined for 9 TCM constituents of Sheng Ji Yu Sui Decoction (SJYSD), and the desired sites for the components were searched in the Drugbank database. and the Sjysd-target network was constructed. Associated targets for Amyotrophic lateral sclerosis (ALS) were then retrieved and collected in the OMIM, TTD, Genecards and DisGeNET databases. Protein-protein interaction and enrichment analysis were performed for the common targets of drugs and diseases, and molecular anchoring for the chosen core targets and related molecules was carried out. The results showed that SJYSD had 100 active compounds corresponding to 598 targets. ALS has a total of 5,325 genes. SJYSD and ALS share 163 genes, and these targets involve PI3K-AKT signaling, p53 signaling and IL-17 signaling, etc. The core components of luteolin and quercetin were discovered and may be used to treat ALS by regulating PI3K-AKT signaling pathway by HSP90AB1 protein.

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## Introduction

Amyotrophic lateral sclerosis (ALS) is a rare, persistent, progressive movement neurological illness that impairs all motor function and muscle control,and has been a thorny clinical challenge of interest to scientists and clinicians since the last 200 years (1). Its main pathological features manifest as damage to both lower and upper motor neurons spanning the motor cortex, the cerebellum, and spinal cord is one of its primary pathogenic hallmarks (2). In addition, defects in neuromuscular connections lead to the breakdown and stagnant skeletal muscle denervation. Progressive muscle atrophy leads to a decrease in j-muscle strength and altered contractile apparatus. All of these processes have been demonstrated to be accompanied by inflammation, which is brought on by the release of harmful substances by activated T cells, ongoing gliosis, which is brought on by activated macrophages, microglia, and astrocytes, and demyelination, which is brought on by injured Schwann cells and oligodendrocytes. Current evidence points to an important role of the innate immune system in ALS, which may be related to microglial cell activation at the site of neurodegeneration (3). Several treatments targeting this mechanism have been proposed, including the use of immunosuppressive drugs to reduce disease progression. However, none of these treatments have shown evidence of altering the progression of the disease (4,5). Both pharmaceutical and non-pharmacological therapies can be used to treat ALS symptoms. For instance, quinidine sulfate and dextromethorphan hydrobromide may enhance bulbar activity. nevertheless, the majority of these ALS symptom treatments are based on those used to treat other diseases rather than being tested in randomized controlled studies (6). In addition, the most commonly used drugs for spasmodic symptoms are muscle relaxants such as baclofen and tizanidine. For ALS patients with excessive salivary secretion, another patient's symptom of anxiety, the clinical use of anticholinergic drugs, such as atropine, scopolamine, amitriptyline, and glycyrrhizate (7,8). Although these drugs have relieved the clinical symptoms and alleviated the pain of ALS patients to some extent, the treatment of ALS is still a thorny problem faced by clinicians due to the strong side effects of these chemicals (9). Therefore, more and more researchers

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are turning their attention to Chinese herbal compounds with milder drug effects, in order to find effective drug combinations against these chronic neurological diseases (10-12). At present, some achievements have been made and important enlightenment has been obtained.

Traditional Chinese medicine has been widely used as an auxiliary means to treat various diseases. Combining pharmacology and systems biology methods, the possible mechanism of network pharmacology to predict the therapeutic effect of traditional Chinese medicine was established (13). Network pharmacology explains the therapeutic features of diseases from their internal causes. Through synergistic multi-compound network pharmacology and drug reuse, precise and effective therapeutic interventions can be achieved, avoiding the need for drug discovery and accelerating clinical transformation (14).

ShengJiYiSui Decoction (SJYSD) is a traditional Chinese medicine compound decoction summarized according to clinical experience. It mainly consists of 7 herbs and 2 animal medicines and has achieved certain effects in the clinical treatment of ALS. However, there are few reports on the treatment of ALS with this compound. Consequently, to investigate the possibility of the mechanism and aim of SJYSD in the therapy of ALS, this research applied network pharmacology and molecular docking technologies. so as to provide a reference for the pharmacological basis of its clinical application.

## Materials and Methods

### Acquiring medication objectives and components

The ingredients of seven herbs *Atractylodes Macrocephala Koidz.*, *Codonopsis Radix*, *Eucommiae Cortex*, *Poria Cocos(Schw.) Wolf.*, *Hedysarum Multijugum Maxim.*, *Chaenomeles Sinensis (Thouin) Koehne*, and *Achyranthis Bidentatae Radix* were retrieved from the TCMSP database (https://tcmsp-e.com/tcmspsearch.php?).. Set ADME parameters to OB≥30%, DL≥0.10, and HL≥4. Screening candidate active ingredients for target fishing. The other two animal drugs *Pulvis cornu cervi* and *Colla carapacis et plastri testudinis* were used to search for the corresponding active ingredients through the HIT2 database (http://hit2.badd-cao.net/). All the targets corresponding to active ingredients were retrieved in the Drugbank database (https://go.drugbank.com/), and the Uniprot database (https://www.uniprot.org/) was used to normalize the names of the targets with "*Homo sapiens*" as the species condition.

### Acquisition of disease targets in ALS

Respectively in the OMIM database (http://www.omim.org/), TTD database (http://bidd.nus.edu.sg/BIDD-Databases/TTD/TTD.asp), Genecards database (https://auth.lifemapsc.com/) and DisGeNET database (https://geneticassociationdb.nih.gov/) with "Amyotrophic lateral sclerosis" as a keyword search, screening of human-related genes, combined with the deletion of repeat value as a data source of ALS related genes.

### Construction of related networks

The series of Network relationships in the study were constructed using Cytoscape 3.2.1 version, and the software's "Network analysis" functionality was used to examine the topological characteristics of the network. The STRING database (https://string-db.org/) is primarily used to build the protein-protein interaction network, and it is from this database that the interaction connection table between nodes is created. Visualization and network topology feature analysis are carried out in Cytoscape.

### Enrichment analysis

The key nodes involved in the research are enriched and analyzed in the DAVID database (https://david.ncifcrf.gov/). The results of enrichment analysis included the GO term (biological process, molecular function, cell composition) and KEGG pathway term. On the basis of $P < 0.01$ screening, visual mapping was performed for the top 20 entries with p values of each term.

### Molecular docking

The core targets and corresponding compounds in the network were simulated by molecular docking. For file preparation, the 3D structures of the substances and proteins were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and the PDB database, respectively. Conduct online molecular docking in the DockThor database (https://dockthor.lncc.br/) and download the docking result file. The docking results were visualized in Pymol software to analyze the binding characteristics between compounds and proteins.

## Results

### Ingredients and targets of ShengJiYiSui decoction

OB≥30%, DL≥0.10, and HL≥4 were set according to the ADME parameters of each compound provided in the TCMSP database. After screening, 10 compounds in *Atractylodes Macrocephala Koidz* were obtained. There are 25 compounds in *Codonopsis Radix*, 21 compounds in *Eucommiae Cortex*, and 14 compounds in *Poria Cocos(Schw.) Wolf.* 23 compounds in *Hedysarum Multijugum Maxim*., 2 compounds in *Chaenomeles Sinensis (Thouin) Koehne*, and 22 compounds in *Achyranthis Bidentatae Radix*. By searching from HIT2 database, it was found that there is only one compound Risedronic Acid in *Pulvis cornu cervi* and *Colla carapacis et plastri testudinis*. The corresponding compound information of each herb is shown in Fig.1A. After the combination of all compounds, it was found that SJYSD had 100 active compounds. A total of 598 SJYSD corresponding targets were obtained through the fishing of compound targets, and the corresponding targets of each compound are shown in Fig.1B.

### Disease targets for ALS

By input keyword "Amyotrophic lateral sclerosis" were obtained 125 genes from the OMIM database, the TTD database obtained 9 genes, the Genecards database obtained 4953 genes, and DisGeNET got 1114 genes. The crossover of genes obtained from different databases is shown in Figure 2.A. ALS-Targets network as shown in Supplementary Fig.1. The intersection of ALS genes with SJYSTD targets yielded a total of 163 possible targets for SJYSD therapy of ALS (Fig.2B). Based on Fig.1B, relevant nodes were extracted to construct the SJYSD-ALS targets network (Fig 2C).

### PPI network establishment and analysis of enrichment

PPI network was constructed for 163 targets in Fig.2C

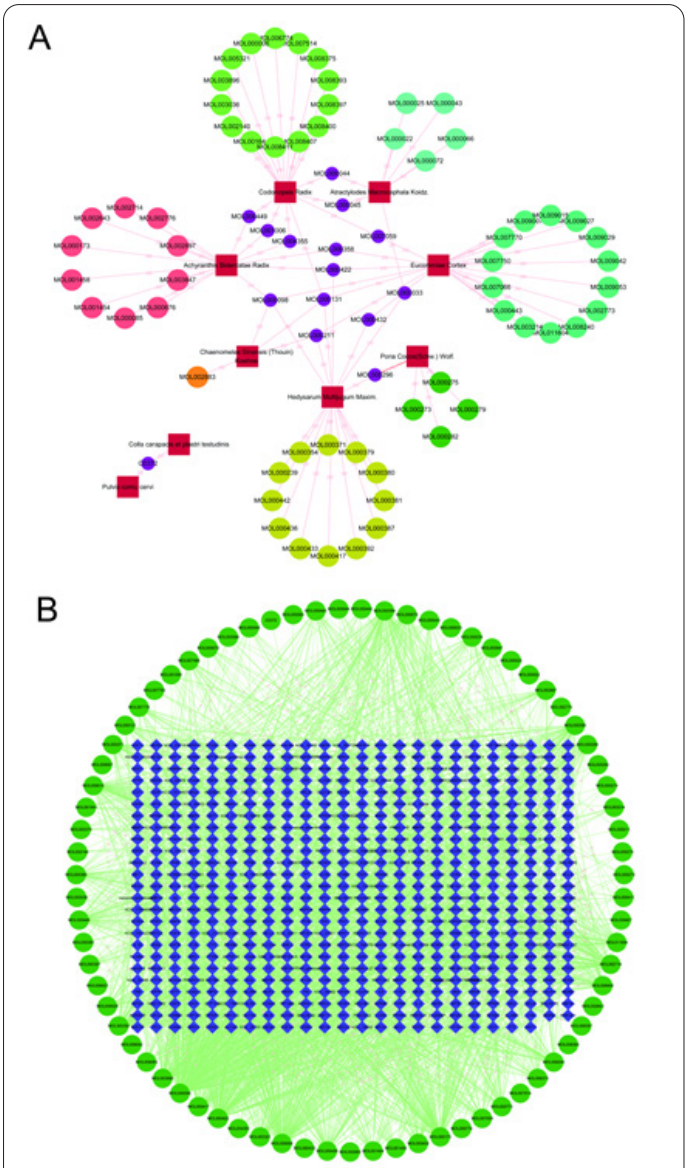


**Figure 1.** Drug-related network. A. Herbal Medicine - Candidate compound Network. Square nodes represent herbs and round nodes represent candidate ingredients. B. Candidate compound - target network. Among them, circular nodes represent candidate components and diamond nodes represent gene targets.

(Fig.3A), and it was found that nodes in the core position of the network included ALB (Degree 116), AKT1 (Degree 114), ACTB (Degree 110), TP53 (Degree 106), etc. After enrichment analysis of these genes, These genes were discovered to be involved in transcription factor complex, macromolecular complex, extracellular space, cytosol, nucleoplasm, etc. (Fig. 3B (b)). negative modulation of the apoptotic process, including in response to hypoxia, in neurons, in aging, etc (Fig.3B (a)). Results The molecular functions involved mainly include enzyme binding, identical protein binding, protein binding, protein kinase binding, etc. (Fig.3B (c)). These genes are connected to the AGE-RAGE signaling route in diabetic complications, the IL-17 signaling pathway, the p53 signaling pathway, and the PI3K-Akt signaling circuit, according to the results of pathway enrichment analysis (Fig 3B (d)).

**The docking of molecules and the construction of a component-target-pathway network**

A composition-target-pathway network was constructed by integrating the relationship between the target pathway and the corresponding target and compound

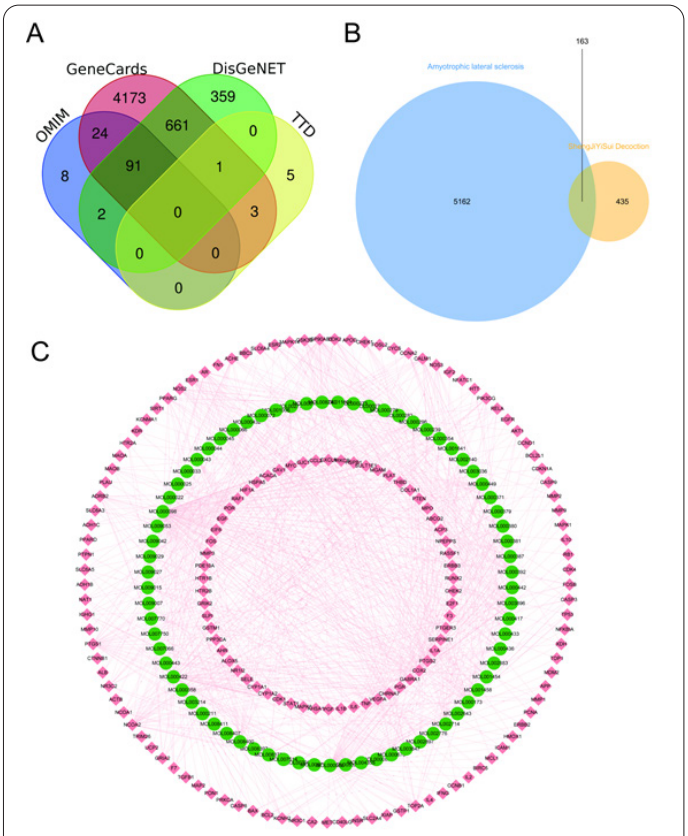


**Figure 2.** A. VENN maps of ALS-related genes obtained from different databases. B. VENN diagram of the intersection of ALS and SJYSD-related targets. C.SJYSD-ALS correlation target network diagram. Among them, green circular nodes represent SJYSD active ingredients, and pink diamond-shaped nodes represent relevant targets of SJYSD in ALS treatment.

**Table 1.** Drug-molecular docking.

| Protein | Molecule | Affinity (kcal/mol) | Protein | Molecule | Affinity |
|---|---|---|---|---|---|
| **AKT1** | MOL000006 | -7.094 | HSP90AB1 | MOL000098 | -9.076 |
| | MOL000098 | -7.115 | | MOL000173 | -8.749 |
| | MOL000173 | -6.813 | | MOL000422 | -8.232 |
| | MOL000422 | -7.076 | PTGS2 | MOL000006 | -8.939 |
| **CALM1** | MOL000173 | -7.331 | | MOL000098 | -8.456 |
| | MOL000422 | -7.137 | | MOL000173 | -7.766 |
| **HSP90AB1** | MOL000006 | -9.020 | | MOL000422 | -7.585 |

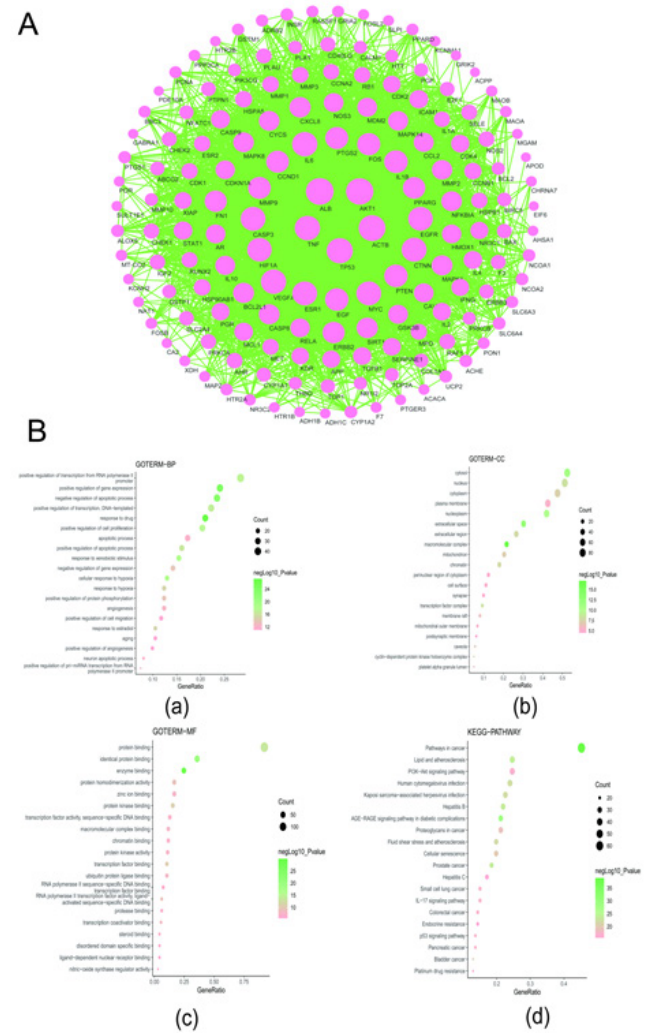


**Figure 3.** A. PPI network diagram of SJYSD-ALS related targets. Among them, the size of the node is rendered according to the Degree value. The larger the Degree, the larger the area of the node. B. Results of SJYSD-ALS-related target enrichment analysis. (a) Biological processes, (b) cell composition, (c) molecular function, and (d) KEGG pathway.

(Fig.4A). The network shows that the SJYSD treatment pathway of ALS involves multiple components, through multiple targets, and involves multiple pathways. Topology analysis on the network found that the average Degree of the network nodes was 11.80233. Nodes with more than twice the Degree were selected to build the core component-target-pathway network (Fig.4B). The network includes 20 nodes, among which 4 component nodes are MOL000006 (luteolin), MOL000098 (quercetin), MOL000173 (wogonin), MOL000422 (kaempferol), 4 target nodes (AKT1, CALM1, HSP90AB1 and PTGS2), 12 pathway nodes. After molecular docking of the related targets and compounds in Fig.4B, it is found that The Affinity of HSP90AB1 with luteolin (Affinity -9.020 kcal/mol) and quercetin (Affinity -9.076 kcal/mol) is most prominent (Tab.1). According to molecular docking visualizations, ASP93, MET98, LEU103, LEU107, ALA111, GLY135, PHE138, TRY139, VAL150, TRP162, THR184, and VAL186 are the binding sites of HSP90AB1 to luteolin (Fig. 4C (a)). LEU48, ASN51, ALA52, ALA55, ASP93, MET98, LEU103, LEU107, GLY108, ILE110, ALA111, GLY135, VAL136, PHE138, TRY139, VAL150, THR184, and VAL186 are the binding sites of HSP90AB1 for quercetin. (Fig.4C (b)).

## Discussion

The most typical neurodegenerative condition that affects neurons responsible for movement is amyotrophic lateral sclerosis (ALS). A number of recent studies have added to our understanding of the pathogenesis of ALS, however, whether the disease is a protein disease, ribose disease, axonal disease, or there is an ongoing debate on a condition connected to the neuronal microenvironment (15).

In this study, we identified luteolin, quercetin, wogonin and kaempferol, four key compounds of SJYSD in the treatment of ALS. Palmitoylglycolamide (PEA) and its complex -- a formulation composed of PEA and the recognized antioxidant flavonoid luteolin via Co-Ultrapealut -- are effective in animal models for intervention in neurodegenerative diseases such as AD. However, the underlying mechanism is still unclear (16). One of the primary mechanisms underlying the advancement of neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, and others is neuroinflammation. Activation of microglia is a major feature of neuroinflammation, promoting the release of pro-inflammatory cytokines and leading to the progressive death of nerve cells. Natural compounds, such as flavonoids, have neuroprotective potential, which may be related to their ability to regulate inflammatory responses in neurodegenerative diseases (17). As a phytochemical with significant biological effects, quercetin has anti-inflammatory, anti-tumor, antioxidant, and neuroprotective properties. According to research, quercetin can activate the AMPK/SIRT1 signaling pathway, lessen endoplasmic reticulum stress, and reduce inflammation and

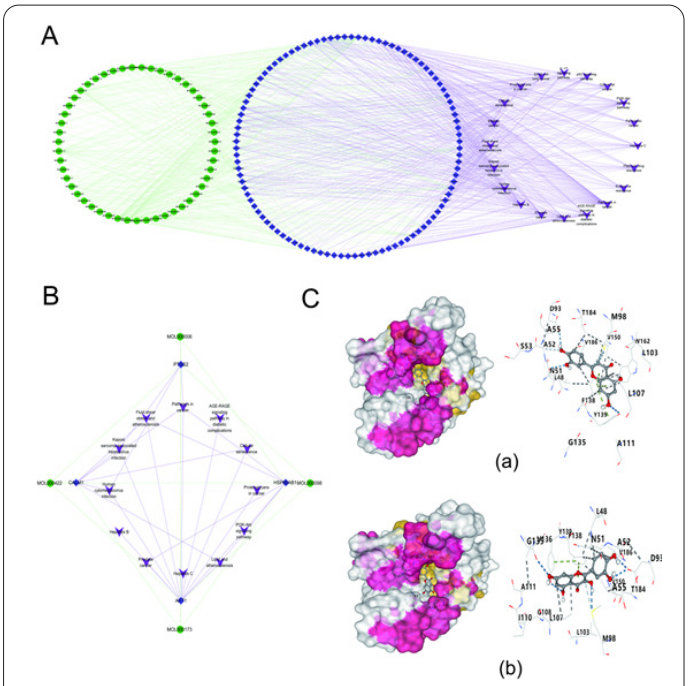


**Figure 4.** A. Component-target-pathway network diagram. The green nodes represent drug components, the blue diamond nodes represent disease targets, and the purple inverted triangle nodes represent pathways. B. Component - target-routing subnetwork of nodes with > 2 degrees in A. C molecular docking results. (a) HSP90AB1f molecular docking luteolin, (b) HSP90AB1 molecular docking quercetin.

apoptosis (18). Kaempferol has been shown to have neuroprotective effects in a number of neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis, through maintaining brain antioxidant enzyme levels, mitochondrial function, and neurogenesis (18). More interestingly, kaempfero has been shown to inhibit SOD1 protein aggregation in familial ALS mutants (G85R) and may be a promising compound for ALS treatment (19).

In this study, we found four core genes of SJYSD in the treatment of ALS, namely AKT1, CALM1, HSP90AB1 and PTGS2. Molecular docking results showed that HSP90AA1 has outstanding binding activity with luteolin and quercetin, and may be a key target for SJYSD treatment of ALS. At present, there is also a small amount of evidence to prove the speculation of this study (20,21). Cyclinf-dependent association and HSP90AB1 ubiquitination lead to cycling-deficiency-mediated partner disorder, which is considered to be possibly related to ALS(21). Their related PI3K-AKT signaling pathway has received our full attention. According to recent research, the PI3K-AKT signaling pathway may be crucial in the development and pathophysiology of ALS (22,23). According to recent research, the PI3K/Akt signaling pathway is involved in ALS and can be influenced by neuroprotective medications to provide protection. For instance, ylphthalein has been proposed as a potential treatment for ALS because it can activate the PI3K/Akt/GSK-3 signaling pathway in ischemic cerebral infarction models, protecting local nerve cells, improving mitochondrial dysfunction, inhibiting apoptosis, and lowering oxidative stress (24-26). Numerous studies have demonstrated that activating the PI3K/Akt pathway improves the survival rate and mitochondrial function of ALS cells by upregulating the expression of anti-apoptotic proteins and downregulating the production of pro-apoptotic proteins (22,23).

In the current investigation, the molecular docking approach was used to confirm the affinity of four important components and four critical proteins, and the research methods of network pharmacology were used to examine the relevant targets and pathways of SJYSD treatment of ALS. It was discovered that HSP90AB1-mediated regulation of the PI3K-AKT signaling pathway by quercetin and luteolin may be used to treat ALS.

## Declarations

### Ethics approval and consent to participate
This study was approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College.

### Consent for publication
Not applicable.

### Availability of data and materials
All data generated or analyzed during this study are included in this published article.

### Competing interests
The authors declare that they have no competing interests.

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### Author contributions
LZ and LY worked together to conceive and design the experiment; SL, YL, HQ and XW completed the data collection together; SL, SM, BM and DW completed the data analysis together; SL wrote and edited the manuscript alone. All authors contributed to manuscript revision, and read and approved the submitted version.

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