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Mechanisms of kudingcha tea in treating Parkinson's disease: a network pharmacology and molecular docking study

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Abstract: *Current PD treatment mainly relies on traditional symptomatic therapy, with new drugs having great potential. Kuding tea, a Chinese medicine with antioxidant properties, might treat PD via antioxidant-driven anti-aging, but its exact mechanism is unclear. This study, combining network pharmacology, differential analysis, PPI network, single-cell analysis, and molecular docking, identified 72 common targets (e.g., CCND1, BCL2L1, PARP1) related to apoptosis, oxidative stress, cell cycle regulation, and the JAK-STAT pathway. Molecular docking confirmed their potential roles, suggesting Kuding tea's components could influence these proteins and pathways, affecting oxidative stress, aging, and inflammation repair in PD treatment, and offering a new research direction for its therapeutic mechanism.*

Keywords: *Kuding tea; Aging; Parkinson's disease; JAK-STAT pathway*

1. Introduction

Parkinson's disease (PD), a common neurodegenerative disease among the middle - aged and elderly, is characterized by the degeneration and massive loss of dopaminergic neurons in the substantia nigra pars compacta of the midbrain, as well as the formation of Lewy bodies[1, 2]. Its complex pathogenesis may be closely related to mitochondrial dysfunction, abnormal protein aggregation, oxidative stress, immune mechanism disorder, and aging[3]. With aging, cell processes prone to neurodegeneration are affected, promoting PD occurrence[4]. The damage from aging may lead to organ dysfunction and accelerate aging - related diseases[5]. In PD research, protecting damaged neurons through anti - aging and apoptosis pathways is significant for uncovering PD's pathogenesis and providing new therapeutic strategies[6, 7].

Multiple studies indicate that Kuding tea's aqueous extract is effective for PD and other neurodegenerative diseases, dilating cerebral blood vessels, improving cerebral blood circulation, and regulating cerebral vascular function[8]. Park Linghua et al. found Kuding tea polysaccharides have strong antioxidant activity in clearing various radicals[9]. Xiong J et al. revealed that Kuding tea polyphenols' antioxidant ability increases with their richness[10]. Zhao X et al. discovered Kuding tea decoction positively impacts mice's immune factor secretion, like interleukin - 2 and interferon. Kakumu Y et al[11]. established mouse models and showed Kuding tea extract's significant anti - inflammatory effect[12]. However, Kuding tea's therapeutic mechanism isn't fully clear and needs more research.

Network pharmacology, integrating systems biology, network biology, computer science, and pharmacology, uses biological network models to analyze "components - genes - targets - diseases" interactions, explaining disease treatment principles and guiding new drug development[13, 14]. Molecular docking technology, based on the lock - and - key principle between drugs and protein molecules, uses computer simulation to explore ligand - receptor interaction sites and magnitudes[15]. This study aims to explore Kuding tea's key mechanisms in PD treatment, constructing "drug - disease - target" association and PPI networks, and conducting in - depth analyses with bioinformatics tools like GO and KEGG, along with molecular docking studies. Our research may reveal Kuding tea's PD treatment mechanism,

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supporting relevant studies and clinical application.

2. Materials and Methods

2.1 Acquisition of Kuding tea tea targets

Structural files of Kuding tea in different formats were obtained from PubChem. Then, databases such as BATMAN-TCM (Score cutoff ≥ 5), PharmMapper, SEA, SuperPred, and Swiss Target Prediction were used to comprehensively collect the potential targets of Kuding tea. The Uniprot database was utilized to standardize the target names, and after removing duplicate information and integrating the data, a Kuding tea target dataset was formed.

2.2 Collection of Parkinson's disease - related genes

High - throughput sequencing data of PD were downloaded from GEO. The “limma” package in R language was used for differential analysis, and the “WGCNA” package was used to construct a weighted gene co - expression network. The screening criteria for differential genes were $|logFC| > 0.3$ and $P < 0.05$. A network model was built using a soft threshold (β), and the co - expression modules most related to the disease were identified. Genes in these modules were extracted and intersected to obtain more reliable and representative PD - related genes. Further, PD - related genes were obtained from databases such as GeneCard, OMIM, TTD, DrugBank, and PharmGKB, and the final PD - related genes were determined after merging and removing duplicates.

2.3 Construction of the “drug - target - disease” network

The intersection of Kuding tea and PD target datasets was taken, and these intersecting targets are likely to be the key targets for Kuding tea in the treatment of PD. The key targets, Kuding tea, and PD - related information were integrated into the Cytoscape 3.9 software to construct an interactive “drug - target - disease” network, which was then visualized.

2.4 Establishment of the PPI network

The key targets were imported into the Cytoscape software. The BisoGenet plugin and CytoNCA plugin were used to construct a PPI network and calculate parameters such as degree centrality (DC) and betweenness centrality (BC). After data screening, the core PPI network was obtained.

2.5 GO function analysis and KEGG pathway analysis

In R3.6.2, multiple Bioconductor packages completed core network gene ID conversion, GO annotation, and KEGG pathway enrichment. Corrected P - value < 0.05 was the screening criterion, selecting the top 10 entries in BP/CC/MF. Cytoscape 3.9 analyzed the top 20 KEGG pathways, building a "gene - pathway" network. Degree centrality visualized Kuding tea's potential PD - treatment targets.

2.6 Molecular docking verification

Autodock Vina verified molecular docking of Kuding tea - related compounds and PD/aging - related key targets. Target protein structures (CCND1, BCL2L1, PARP1, STAT1) came from RCSB PDB. Proteins were processed (removing water/ligands, adding hydrogen) using Autodock Tools1.5.7 to prepare PDBQT files. Kuding tea component 2D structures (quercetin, kaempferol, β - sitosterol) were from PubChem, hydrogen - added, then docked. The docking pocket covered all potential protein active sites, with multiple conformations compared. The lowest - binding - energy conformation was chosen. Pymol analyzed and displayed ligand - receptor interactions.

3. Results

3.1 Identification of Active Ingredients and Targets of Kuding tea tea

In TCMSP, we retrieved the SMILES code of Kuding tea by keyword search and screened out its

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target genes and proteins. The criteria were OB% ≥ 30 and DL ≥ 0.18. The drug target prediction results were from high - evidence experimental studies and related literature. The predicted drug target proteins in the TCMS database were converted into gene names via the Uniprot database. Finally, the "venn" package in R software was used to intersect these target genes and remove duplicates, which were considered as the target genes related to Kuding tea. Eight active components were identified from Kuding tea, and 149 key target genes were precisely identified using the UniProt database (as shown in Table 1).

Table 1 Basic Information Table of Partial Active Ingredients of Kuding tea Tea

Serial Number	MOL-ID	Component English Name
1	MOL000211	Mairin
2	MOL000358	beta-sitosterol
3	MOL000363	amyrin Palmitate
4	MOL000422	kaempferol
5	MOL000492	(+)-catechin
6	MOL006504	(-)-Catechin gallate
7	MOL006554	Taraxerol
8	MOL000098	quercetin

3.2 Parkinson's disease - related targets

The GEO and CellAge databases were collected to obtain the combined de-emphasis of the disease targets of GSE7621 and aging for PD, which were 1,918 and 1,259, respectively, and 9,227 genes were de-emphasised for the two kinds of diseases combined.

3.3 Network diagram of active ingredients and common targets between Kuding tea tea and Parkinson's disease

The GSE7621 expression matrix was normalized and analyzed via principal component analysis. Using thresholds of adjusted |log(FC)| > 0.3 and p - value < 0.05, 21604 DEGs were identified in the training set. These DEGs were visualized using volcano plots, heatmaps, and differential expression ranking plots. The targets of Kuding tea's active ingredients and PD were input into the "Venn Diagram" package in R language, yielding a Venn diagram that revealed 72 common targets. Based on these intersecting targets, we further screened the active ingredients in the candidate compounds associated with these targets.

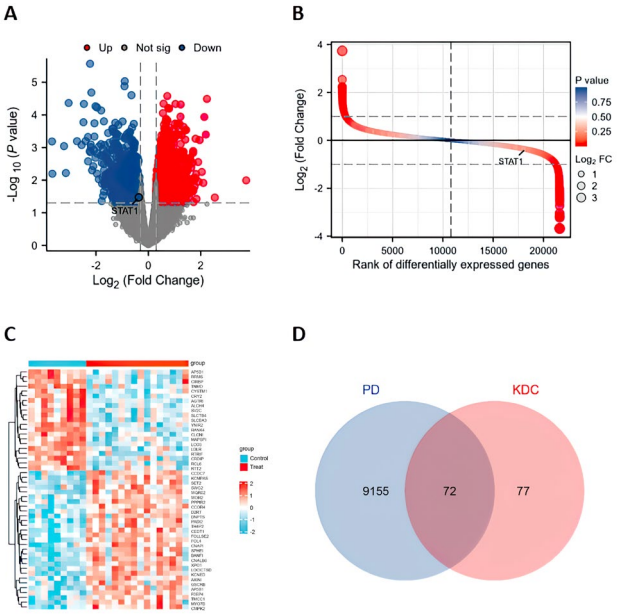

Figure 1 Identification of DEGs and DESRGs in the GSE7621 training set for PD (A) Volcano plot, (B) Differential expression ranking plot, (C) Heatmap, (D) Venn diagram showing the overlap between PD - related genes and genes in the Kuding tea tea database.

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3.4 Visualization of the Relationship between the Main Active Ingredients of Kuding tea Tea and Their Targets

The MOL - ID and corresponding target data of the main active ingredients of Kuding tea tea (see Table 1) were imported into Cytoscape 3.9 software. A visual network was constructed, showing the relationship between the active ingredients in Kuding tea tea and their targets. In this network, each node represents Kuding tea tea, its active ingredients, Parkinson's disease (PD), and related targets, while the edges reveal the interconnections between these nodes. This network diagram provides a comprehensive perspective for understanding how Kuding tea tea interacts with specific targets through its active ingredients, thereby affecting Parkinson's disease (as shown in Figure 2).

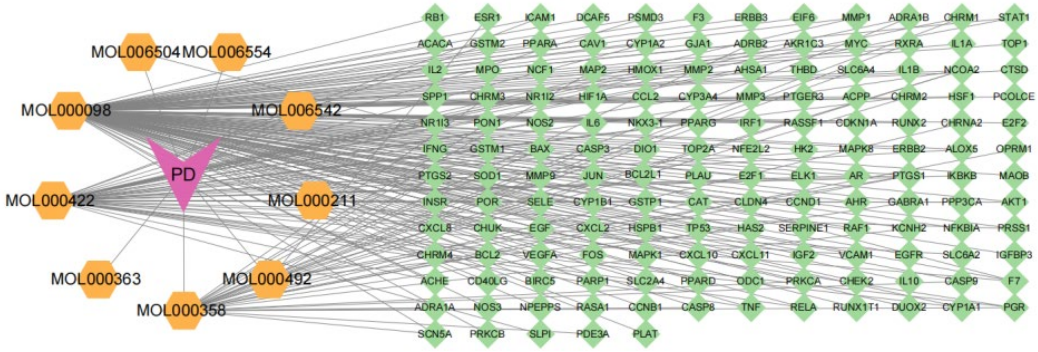

Figure 2 The "drug - active components - common targets - disease" network of Kuding tea in the treatment.

3.5 The protein-protein interaction network diagram of the interaction between the active components of Kuding tea and the key target proteins of neurodegenerative diseases

Using the STRING database, a PPI network based on common targets of Kuding tea and PD was constructed (Figure 1). It has 28 nodes, 72 edges, and an average degree of 5.14, indicating complex interactions. A topological analysis of the PPI was done (Figure 3). Genes with betweenness centrality > 10 were considered core targets. Based on degree values, 14 key targets were identified: CCND1, BCL2L1, ICAM-1, IGFBP3, CDKN1A, MMP3, TOP1, F3, PLAT, STAT1, PARAP1, CXCL10, and CCNB1. These genes rank highest in degree values in the PPI network (Figure 4), suggesting their importance. They may be crucial targets for PD treatment, offering new potential directions.

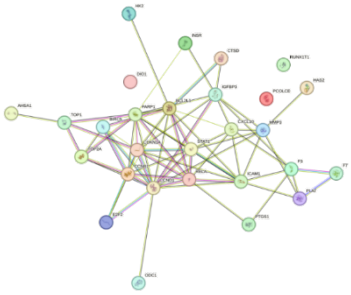

Figure 3 Protein-Protein Interaction.

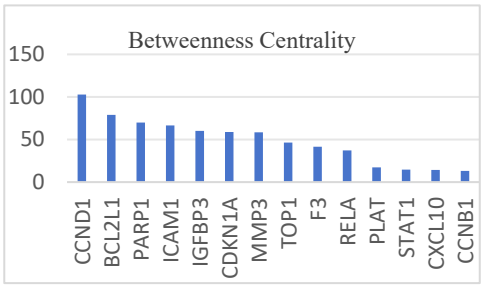

Figure 4 Betweenness Centrality of Relevant Targets.

3.6 GO Functional Analysis and KEGG Pathway Enrichment Analysis of Kuding tea Targets for Parkinson's Disease

Based on the STRING database, a comprehensive Gene Ontology (GO) enrichment analysis of the potential targets of Kuding tea for the treatment of Parkinson's disease (PD) was conducted, covering three dimensions: biological processes, molecular functions, and cellular components. After screening, items with an adjusted P-value less than 0.05 were identified. The results show that these targets are involved in a total of 1,458 biological processes and are associated with 167 molecular functions and 109 cellular components (see Figure 5). These targets are primarily closely related to the activity of G-protein coupled receptors, the activation of hormone receptors, the binding of nuclear hormones, the reactive

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activity of cytokine and mucin receptors, and the function of postsynaptic neurotransmitter receptors. The same method was used to perform KEGG pathway enrichment analysis on the potential target genes, and a total of 76 signaling pathways were enriched, as shown in Figure 6. The results indicate that the apoptosis pathway, JAK-STAT signaling pathway, liver cancer signaling pathway, and the synthesis, secretion, and action pathway of growth hormone are significantly enriched, involving a large number of genes and having a high enrichment factor.

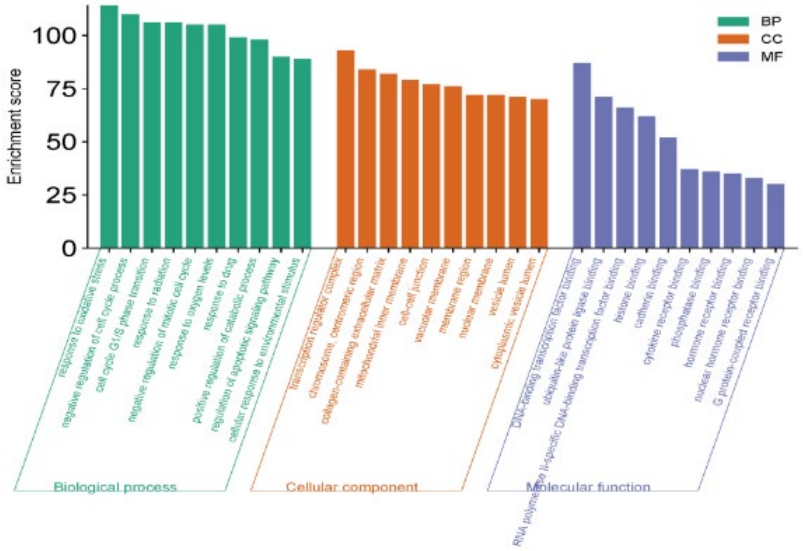

Figure 5 GO Analysis of Potential Therapeutic Targets of Kuding tea for PD.

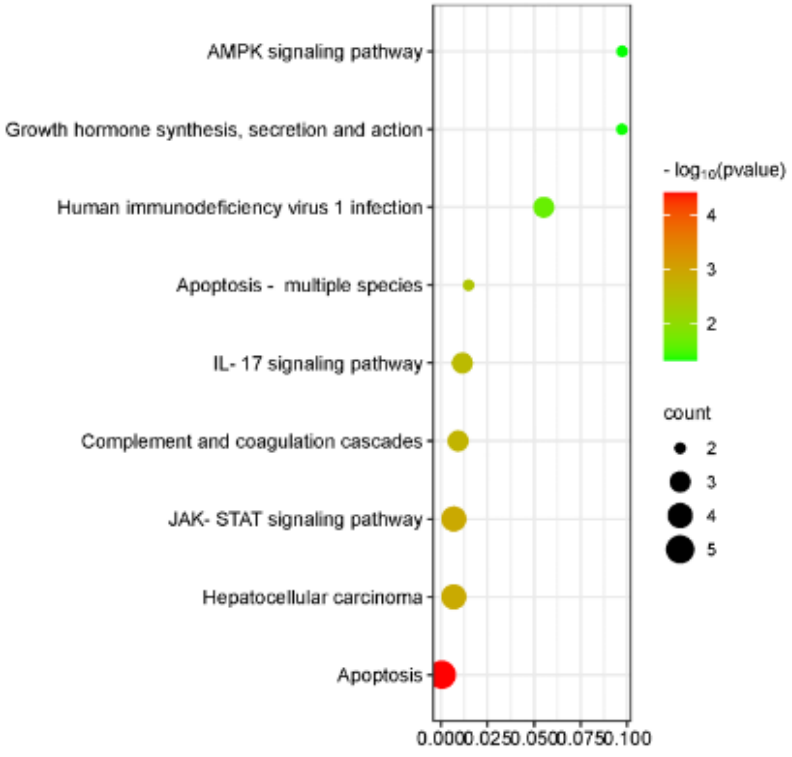

Figure 6 KEGG pathway enrichment analysis of potential therapeutic targets of Kuding tea for PD.

3.7 Molecular Docking Validation

To verify the predicted targets of Kuding tea - related compounds, AutoDock Vina was used for molecular docking of representative compounds (quercetin, kaempferol, β - sitosterol) with key target proteins (CCND1, BCL2L1, PARP1, STAT1). Twelve active components with binding energy ≤ -5.3 kcal/mol were obtained, showing strong affinity. The lowest - binding - energy conformation was chosen.

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Table 2 details the binding energies（as shown in Table 2）, and Figure 7 shows ligands' positions and interactions. Results showed quercetin, kaempferol, and β - sitosterol could form hydrogen bonds with targets. Kaempferol had the most interactions and stable binding. Kaempferol has anti - inflammatory, antioxidant effects, and protects mitochondria. Its antioxidant effect in the nervous system can improve memory impairments from neurodegenerative changes. These results indicate Kuding tea's active components may exert therapeutic or ameliorating effects on PD via these targets.

Table 2 Binding energy of key component and key targets (kcal/mol).

Compound	Target			
	STAT1	CCND1	BCL2L1	RARP1
Quercetin	- 6.5	- 9.2	- 7.6	- 8.7
Kaempferol	- 6.3	- 8.5	- 8.1	- 8.8
β-sitosterol	- 5.3	- 6.5	- 6.4	- 5.4

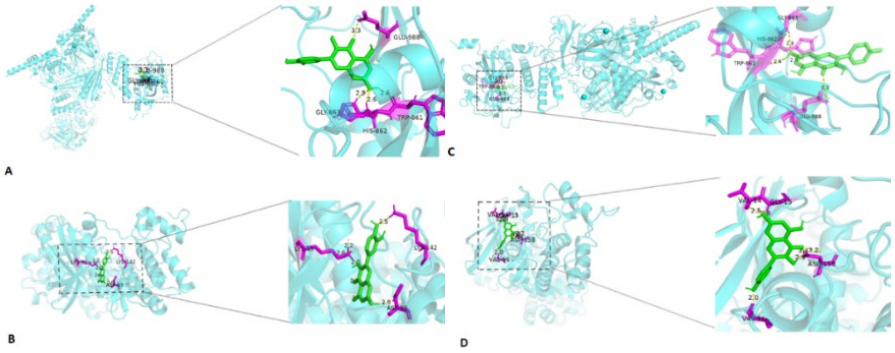

Figure 7 Molecular docking pattem ofkey target and component. A. Optimal docking conformation of quercetin with PARP1; B. Optimal docking conformation of quercetin with CCND1; C. Optimal docking conformation of kaempferol with PARP1; D. Optimal docking conformation of kaempferol with CCND1.

4. Discussion

Parkinson's Disease (PD) is a complex neurodegenerative disorder with multiple pathological mechanisms[16, 17]. Current pharmacological treatments can slow neuronal dysfunction but cannot reverse damage once the disease is in middle/late stages[16]. In Traditional Chinese Medicine (TCM), PD symptoms are categorized into syndromes like "dementia," "tremor," and "hemiplegia," with treatment strategies focusing on resolving phlegm, opening orifices, and invigorating the mind[18].

Kuding tea contains various active components, including triterpenes, flavonoids, amino acids, volatile oils, and polysaccharides[19]. Studies show it can alleviate symptoms like dizziness, headache, and fatigue, while also having effects on lowering blood pressure and improving blood flow[20]. Research suggests Kuding tea may have therapeutic effects on PD through multiple components and targets, including CCND1, BCL2L1, PARP1, ICAM1, IGFBP3, TOP3, STAT1, CXCL10, and CCNB1. Quercetin, a key component, has demonstrated neuroprotective effects in PD models by promoting autophagy, reducing cell death, and improving neuronal survival[17]. The combination of quercetin and piperine has shown strong neuroprotective effects against MPTP-induced motor disorders, oxidative stress, and neuroinflammation.Kuding tea's antioxidant properties are significant, with its n-butanol extract protecting cells from hydrogen peroxide-induced toxicity by enhancing antioxidant enzyme activity and reducing oxidative damage[21]. The aqueous extract mitigates oxidative damage in vascular endothelial cells and prevents oxidative aging in mice.Kuding tea also demonstrates immunomodulatory effects, increasing antibody production, enhancing phagocytic capacity, and boosting natural killer cell activity[22]. It can promote the secretion of interleukin-2 and interferon, improving immune function.In neuroprotection, quercetin reduces dopaminergic neuron loss, decreases lipid peroxidation, and increases antioxidant levels in PD models[23, 24]. It also regulates ion transport mechanisms and upregulates anti-apoptotic genes to slow neurodegenerative changes[25].

In summary, Kuding tea and its components show multifaceted potential in PD treatment through antioxidant, anti-inflammatory, immunomodulatory, and neuroprotective effects. Future research should explore Kuding tea's application in PD treatment to provide a scientific basis for developing novel therapeutic agents.

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References

[1] HAYES M T. Parkinson's Disease and Parkinsonism [J]. Am J Med, 2019, 132(7): 802-7.
[2] KALIA L V, LANG A E. Parkinson's disease [J]. Lancet, 2015, 386(9996): 896-912.
[3] LOTANKAR S, PRABHAVALKAR K S, BHATT L K. Biomarkers for Parkinson's Disease: Recent Advancement [J]. Neurosci Bull, 2017, 33(5): 585-97.
[4] FEARNLEY J M, LEES A J. Ageing and Parkinson's disease: substantia nigra regional selectivity [J]. Brain, 1991, 114 (Pt 5)(2283-301.
[5] REEVE A, SIMCOX E, TURNBULL D. Ageing and Parkinson's disease: why is advancing age the biggest risk factor? [J]. Ageing Res Rev, 2014, 14(100): 19-30.
[6] TRIST B G, HARE D J, DOUBLE K L. Oxidative stress in the aging substantia nigra and the etiology of Parkinson's disease [J]. Aging Cell, 2019, 18(6): e13031.
[7] MATTSON M P, ARUMUGAM T V. Hallmarks of Brain Aging: Adaptive and Pathological Modification by Metabolic States [J]. Cell Metab, 2018, 27(6): 1176-99.
[8] SONG C, YU Q, LI X, et al. The Hypolipidemic Effect of Total Saponins from Kuding Tea in High-Fat Diet-Induced Hyperlipidemic Mice and Its Composition Characterized by UPLC-QTOF-MS/MS [J]. J Food Sci, 2016, 81(5): H1313-9.
[9] LIU B, MA R, ZHANG J, et al. Preventive Effect of Small-Leaved Kuding Tea (Ligustrum robustum (Roxb.) Bl.) Polyphenols on D-Galactose-Induced Oxidative Stress and Aging in Mice [J]. Evid Based Complement Alternat Med, 2019, 2019(3152324.
[10] XIONG J, LIU X H, BUI V B, et al. Phenolic constituents from the leaves of Cratoxylum formosum ssp. pruniflorum [J]. Fitoterapia, 2014, 94(114-9.
[11] ZHAO X, SONG J L, YI R, et al. Comparison of Antioxidative Effects of Insect Tea and Its Raw Tea (Kuding Tea) Polyphenols in Kunming Mice [J]. Molecules, 2018, 23(1)
[12] KAKUMU Y, NGUYEN T M T, YAMAUCHI K, et al. New benzoic acid and caffeoyl derivatives with anti-inflammatory activities isolated from leaves of Ilex kaushue [J]. Nat Prod Res, 2022, 36(12): 3013-21.
[13] ZHAO L, ZHANG H, LI N, et al. Network pharmacology, a promising approach to reveal the pharmacology mechanism of Chinese medicine formula [J]. J Ethnopharmacol, 2023, 309(116306.
[14] NOOR F, ASIF M, ASHFAQ U A, et al. Machine learning for synergistic network pharmacology: a comprehensive overview [J]. Brief Bioinform, 2023, 24(3)
[15] ZHANG P, ZHANG D, ZHOU W, et al. Network pharmacology: towards the artificial intelligence-based precision traditional Chinese medicine [J]. Brief Bioinform, 2023, 25(1)
[16] KUMAR S, BEHL T, SEHGAL A, et al. Exploring the Role of Orexinergic Neurons in Parkinson's Disease [J]. Neurotox Res, 2021, 39(6): 2141-53.
[17] SALAMA R M, DARWISH S F, YEHIA R, et al. Apilarnil exerts neuroprotective effects and alleviates motor dysfunction by rebalancing M1/M2 microglia polarization, regulating miR-155 and miR-124 expression in a rotenone-induced Parkinson's disease rat model [J]. Int Immunopharmacol, 2024, 137(112536.
[18] CHEN P, ZHANG J, WANG C, et al. The pathogenesis and treatment mechanism of Parkinson's disease from the perspective of traditional Chinese medicine [J]. Phytomedicine, 2022, 100(154044.
[19] WüPPER S, LüERSEN K, RIMBACH G. Chemical Composition, Bioactivity and Safety Aspects of Kuding Tea-From Beverage to Herbal Extract [J]. Nutrients, 2020, 12(9)
[20] JIANG Z, LU Z, WANG T, et al. Lipid-Lowering Efficacy of Kuding Tea in Patients With Metabolic Disorders: A Systematic Review and Meta-Analysis of Randomized Controlled Trials [J]. Front Nutr, 2022, 9(802687.
[21] CHOONG C J, MOCHIZUKI H. Neuropathology of α-synuclein in Parkinson's disease [J]. Neuropathology, 2022, 42(2): 93-103.
[22] SINGH S, JAMWAL S, KUMAR P. Neuroprotective potential of Quercetin in combination with piperine against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity [J]. Neural Regen Res, 2017, 12(7): 1137-44.
[23] SONG X, LI C Y, ZENG Y, et al. Immunomodulatory effects of crude phenylethanoid glycosides from Ligustrum purpurascens [J]. J Ethnopharmacol, 2012, 144(3): 584-91.
[24] CHIANG M C, TSAI T Y, WANG C J. The Potential Benefits of Quercetin for Brain Health: A Review of Anti-Inflammatory and Neuroprotective Mechanisms [J]. Int J Mol Sci, 2023, 24(7)
[25] ACıKARA O B, KARATOPRAK G, YüCEL Ç, et al. A Critical Analysis of Quercetin as the Attractive Target for the Treatment of Parkinson's Disease [J]. CNS Neurol Disord Drug Targets, 2022, 21(9): 795-817.