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네트워크 약리학 기반 복령의 뇌전증 작용 기전 예측 및 임상적 시사점

윤선우[1] · **최서연**[2] · **김태환**[2] · **한주희**[2] · **방미란**[3] · **장규태**[1,3] · **이진용**[4] · **김효인**[5] · **이동헌**[6,*] · **이선행**[1,2,*]

[1]경희대학교 대학원 소아과학교실, [2]경희대학교 한방병원 한방소아과, [3]강동경희대학교 한방병원 한방소아과,
[4]한국한의학연구원, [5]경희대학교 중점연구소, [6]가천대학교 한의과대학 본초약리학교실

Abstract

Network pharmacology-based prediction of the molecular mechanisms and its clinical implications of *Poria cocos* in epilepsy

Yoon Seon Woo[1] · **Choi Seo Yeon**[2] · **Kim Tae Hwan**[2] · **Han Ju Hui**[2] · **Bang Mi Ran**[3] · **Chang Gyu Tae**[1,3] · **Lee Jin Yong**[4] · **Kim Hyo In**[5] · **Lee Dong Hun**[6,*] · **Lee Sun Haeng**[1,2,*]

[1]*Department of Korean Pediatrics, Graduate School, Kyung Hee University,*
[2]*Department of Korean Pediatrics, Kyung Hee University Medical Center,* [3]*Department of Korean Pediatrics, College of Korean Medicine, Kyung Hee University, Kyung Hee University Hospital at Gangdong,*
[4]*Korea Institute of Oriental Medicine,* [5] *Core Research Institute (CRI), Kyung Hee University,*
[6]*Department of Herbal Pharmacology, College of Korean Medicine, Gachon University*

Objectives

This study aimed to elucidate the molecular mechanisms and key targets of Poria cocos in epilepsy using a network pharmacology approach and to explore its clinical implications.

Methods

The active compounds of *P. cocos* and their corresponding targets were identified using the Traditional Chinese Medicine Systems Pharmacology Database (TCMSP) and SwissTargetPrediction databases. Epilepsy-related genes were retrieved from the GeneCards database. A protein-protein interaction (PPI) network was constructed via STRING, and key targets were identified through topological analysis. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed to explore biological functions and pathways.

Results

Among the 241 putative targets of *P. cocos,* 175 (72.6%) overlapped with epilepsy-associated genes. PPI network analysis identified 25 core targets, including AKT1, MAPK3, EGFR, TNF, and BCL2. GO enrichment analysis highlighted regulation of blood vessel endothelial cell migration and ligand-activated transcription factor activity. KEGG pathways were significantly enriched in VEGF signaling, lipid and atherosclerosis, and prostate cancer pathways.

Conclusions

P. cocos may influence epilepsy-related biological networks by modulating multiple targets and signaling pathways related to neuroinflammation, apoptosis, and vascular regulation. These findings provide a molecular basis for its traditional use and suggest its potential as a multi-target therapeutic agent for epilepsy.

Key words: Poria cocos, Epilepsy, Network pharmacology, Protein–protein interaction, Multi-target therapy

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*Corresponding Author 1: Lee Sun Haeng
Address: Department of Korean Pediatrics, College of Korean Medicine, Kyung Hee University, 26-6, Kyungheedae-ro, Dongdaemun-gu, Seoul, Republic of Korea
Tel: +82-2-958-9167 / Fax: +82-2-958-9169 / E-mail: civil011@khu.ac.kr
*Corresponding Author 2: Lee Donghun
Address: Department of Herbal Pharmacology, College of Korean Medicine, Gachon University, 1342 Seongnamdae-ro, Sujeong-gu, Seongnam 13120, Gyeonggi-do, Republic of Korea
Tel: +82-31-750-5415 / Fax: +82-31-750-5415 / E-mail: dlee@gachon.ac.kr

Ⅰ. Introduction

Epilepsy is a common chronic neurological disorder in childhood, affecting approximately 0.5–1% of the global pediatric population[1]. In Korea, data from the Health Insurance Review and Assessment Service (HIRA) indicate a steady increase in epilepsy-related medical visits (International Classification of Diseases-10 code G40), reaching 151,510 cases by 2024, with patients aged <20 years accounting for 20% of the total[2]. Approximately 30% of children with epilepsy continue to experience seizures into adulthood, emphasizing the importance of early diagnosis and timely therapeutic intervention[3]. Although 70–80% of pediatric patients achieve seizure control with antiepileptic drugs (AEDs), 20–30% develop drug-resistant epilepsy (DRE), which often leads to secondary complications, such as cognitive impairment, developmental delay, and learning disabilities[4].

Currently, the first-line treatment for epilepsy is pharmacological and primarily involves AEDs. The ketogenic diet, resective brain surgery, and vagus nerve stimulation are considered for drug-resistant cases[5]. However, these options are limited by factors, such as dietary compliance, surgical invasiveness, and accessibility to neuromodulation devices. Therefore, complementary approaches within traditional medicine, particularly herbal therapy and acupuncture, are gaining increasing attention. Recent meta-analyses have shown that the combination of herbal medicine and acupuncture significantly reduces treatment failure rates and adverse effects in pediatric epilepsy[6], and some studies have suggested enhanced efficacy and safety of herbal medicine alone or in combination with AEDs[7].

Poria cocos (Schwein.) Wolf, a saprophytic fungus that grows on pine roots, has been widely used in East Asian traditional medicine for centuries to treat various conditions. In Korean medicine, *P. cocos* is traditionally used to promote diuresis (利水滲濕), strengthen the spleen (健脾), and calm the mind (寧心安神)[8]. Owing to its sedative and neuroprotective effects, it is frequently prescribed in formulas for epilepsy. A clinical study involving 930 children with epilepsy reported that a herbal capsule containing *P. cocos* significantly reduced seizure frequency and duration, possibly through the modulation of brain electrical activity[9]. Pharmacological studies have identified triterpenoids as the major bioactive compounds in *P. cocos*, with antiepileptic effects demonstrated in maximal electroshock seizure and pentylenetetrazol induced seizure models, likely through the enhancement of gamma-aminobutyric acid–ergic transmission and the reduction of excitatory neurotransmitters[10]. An analysis of 159 classical prescriptions listed in nine Korean traditional medical texts approved by the Ministry of Food and Drug Safety revealed that *P. cocos* appeared 36 times, ranking fifth among the frequently used herbs. It also showed a high betweenness centrality (2.1), suggesting the central role of *P. cocos* in herbal formulations[11]. A separate analysis of clinical case reports on epilepsy found that *P. cocos* is the second most frequently prescribed herb after *Glycyrrhiza uralensis*, further highlighting its significance in traditional therapeutic strategies[12].

Network pharmacology is a research approach that enables an integrative analysis of interactions among drugs, targets, and diseases, thereby facilitating the understanding of complex biological mechanisms. This methodology has gained increasing attention in traditional medicine research, as it allows for the interpretation of herbal medicines' multi-component, multi-target, and multi-pathway effects beyond the conventional “one drug-one target” paradigm[13].

In epilepsy research, network pharmacology has been actively utilized to elucidate the antiepileptic mechanisms of traditional herbal formulas such as Kanghantang (康癎湯), including modulation of neurotransmitter systems and inhibition of neuroinflammatory pathways[14]. It has also been used to identify synergistic drug combinations, such as levetiracetam and topiramate, demonstrating improved seizure suppression through network-based predictions[15].

Epilepsy is a serious disorder that can have long-term effects on neurodevelopment and learning in children, thus requiring a multidimensional and systematic therapeutic approach. *P. cocos*, which has a long history of traditional use and growing modern pharmacological evidence, is considered a promising candidate for the treatment of epilepsy. However, comprehensive analyses of in-

teractions between various bioactive constituents and epilepsy-related molecular networks remain limited.

Therefore, the present study aimed to investigate the molecular mechanisms of action of *P. cocos* in the context of epilepsy using a network pharmacology approach. By identifying its active compounds, target proteins, and associated signaling pathways, we sought to scientifically evaluate its possible mechanistic relevance and provide foundational insights that may inform future preclinical and clinical research.

Ⅱ. Materials and Methods

1. Identification and Screening of Bioactive Compounds in *P. cocos*

The Traditional Chinese Medicine Systems Pharmacology Database (TCMSP) was used to identify the bioactive compounds of *P. cocos* with potential pharmacological activity. The search term "Poria cocos (Schw.) Wolf" was applied. Candidate compounds were filtered based on oral bioavailability (OB) $\geq$ 30% and drug-likeness (DL) $\geq$ 0.1813). The molecular structures and PubChem IDs of selected compounds were retrieved from the PubChem database.

2. Prediction of Potential Targets of Active Compounds

The potential protein targets of the selected compounds were predicted using the SwissTargetPrediction database. PubChem IDs of each compound were entered, and predicted targets with a probability score of zero were excluded. The compound-target interaction network was constructed and visualized using Cytoscape (v3.10.3).

3. Collection of Epilepsy-Associated Target Genes

To obtain epilepsy-related genes and proteins, the Gene Cards database (https://www.genecards.org/) was queried with the keyword “epilepsy.” Relevant biological targets associated with epilepsy were identified for further analysis.

4. Identification of Common Targets and Construction of a Protein–Protein Interaction (PPI) Network

Common targets of *P. cocos* and epilepsy were identified using Venny 2.1.0. These overlapping targets were analyzed for PPIs using the STRING database (https://string-db.org/), specifying “Homo sapiens” as the organism and a confidence score threshold of $\geq$0.700 (highest confidence). The resulting PPI network was visualized using Cytoscape (v3.10.3) and topological analysis was performed using the CytoNCA plugin (v2.1.6). Core genes were defined as those with values above the mean for degree centrality (DC), betweenness centrality (BC), closeness centrality (CC), and eigenvector centrality (EC).

5. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway Enrichment Analyses

Functional enrichment analysis was performed using the ClueGO plugin (v2.5.10) in Cytoscape to explore the biological processes and signaling pathways associated with overlapping and core targets. The enrichment parameters were set as $p \leq 0.05$ and kappa score ≥ 0.7. Statistically significant GO terms and KEGG pathways were selected based on the False Discovery Rate (FDR), allowing a comprehensive understanding of the potential molecular mechanisms of *P. cocos* in the treatment of epilepsy.

Ⅲ. Results

1. Identification of Active Compounds and Target Proteins of *P. cocos*

Among the 15 compounds initially retrieved, four lacking PubChem IDs were excluded, and 11 compounds were selected for further analysis (Table 1).

Table 1. Active Compounds of Poria cocos (Schwein.) Wolf and Their Molecular Structure.

	Active Compound	MW	OB(%)	DL	PubChem ID
1	(2R)-2-[(3S,5R,10S,13R,14R,16R,17R)-3,16-dihydroxy-4,4,10,13,14-pentamethyl-2,3,5,6,12,15,16,17-octahydro-1H-cyclopenta[a]phenanthren-17-yl]-6-methylhept-5-enoic acid	470.76	30.98	0.81	10743008
2	trametenolic acid	456.78	38.71	0.80	125181708
3	7,9(11)-dehydropachymic acid	526.83	35.11	0.81	15226717
4	Cerevisterol	430.74	37.96	0.77	10181133
5	(2R)-2-[(3S,5R,10S,13R,14R,16R,17R)-3,16-dihydroxy-4,4,10,13,14-pentamethyl-2,3,5,6,12,15,16,17-octahydro-1H-cyclopenta[a]phenanthren-17-yl]-5-isopropyl-hex-5-enoic acid	484.79	31.07	0.82	15225964
6	ergosta-7,22E-dien-3beta-ol	398.74	43.51	0.72	5283628
7	Ergosterol peroxide*	430.74	40.36	0.81	-
8	(2R)-2-[(5R,10S,13R,14R,16R,17R)-16-hydroxy-3-keto-4,4,10,13,14-pentamethyl-1,2,5,6,12,15,16,17-octahydrocyclopenta[a]phenanthren-17-yl]-5-isopropyl-hex-5-enoic acid	482.77	38.26	0.82	9805290
9	3beta-Hydroxy-24-methylene-8-lanostene-21-oic acid	470.81	38.70	0.81	73402
10	pachymic acid*	528.85	33.63	0.81	-
11	Poricoic Acid A	498.77	30.61	0.76	5471851
12	Poricoic acid B	484.74	30.52	0.75	5471852
13	Poricoic Acid C	482.77	38.15	0.75	56668247
14	hederagenin*	414.79	36.91	0.75	-
15	dehydroeburicoic acid*	453.75	44.17	0.83	-

*MW, molecular weight; OB, oral bioavailability; DL, drug-likeness.

Using the PubChem IDs of the selected compounds, the protein targets were predicted using the SwissTarget Prediction platform. After removing the duplicates and proteins with a prediction probability of zero, 241 valid target proteins were identified (Appendix 1). A network comprising 11 compounds and their associated 241 target proteins was constructed, resulting in a network of 241 nodes and 749 edges (Figure 1A).

2. Collection of Epilepsy–Related Target Proteins and Identification of Overlapping Genes

To identify disease-associated targets, the keyword “epilepsy” was searched in the GeneCards database, yielding 9,586 epilepsy-related genes. Venn diagram analysis using Venny 2.1.0 identified 175 overlapping genes between the targets of P. cocos and epilepsy-associated genes. This corresponded to a 72.61% overlap between the two datasets (Figure 1B).

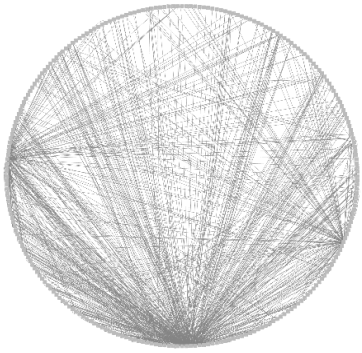

Figure 1A. Network of *poria cocos* with 241 nodes and 749 edges.

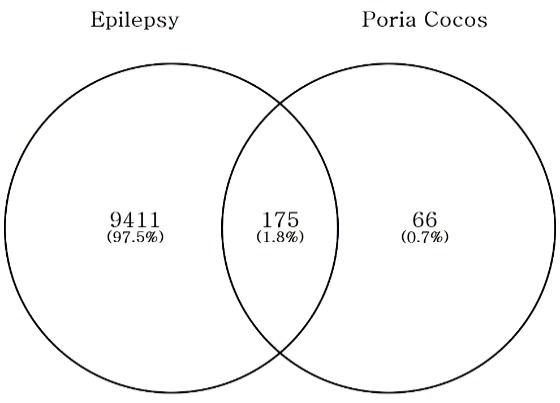

Figure 1B. Venn diagram of intersection targets between *poria cocos* network and the gene sets of epilepsy.

3. Construction of PPI Network and Identification of Core Genes

To elucidate the interactions between overlapping targets, 175 common genes were entered into the STRING database. The parameters were set as Organism: Homo sapiens and Interaction Score: ≥0.700 (high confidence). The PPI network was visualized using Cytoscape v3.10.3, and consisted of 161 nodes and 470 edges (Figure 2).

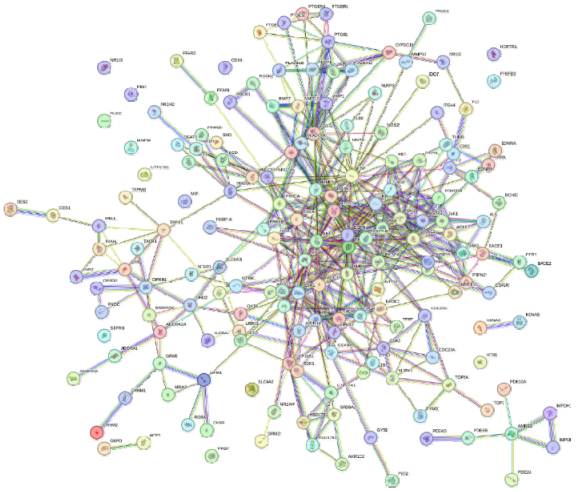

Figure 2. Network of common genes of *poria cocos* and epilepsy.

CytoNCA v2.1.6 was applied to perform centrality analysis and extract the key nodes. Degree Centrality (DC), Betweenness Centrality (BC), Closeness Centrality (CC), and Eigenvector Centrality (EC) were calculated and proteins exceeding the average in all four metrics were defined as core genes. Based on these criteria, 25 core proteins were identified (Table 2).

Table 2. Coregenes of PPI Network of Intersection Targets between Epilepsy and *Poria Cocos*.

	7Degree	Eigenvector	Betweenness	Closeness
EGFR	32	0.3206094	2458.0745	0.075686
AKT1	30	0.3116239	3104.0554	0.076227
ESR1	27	0.23618919	4188.469	0.075401
TNF	27	0.22124952	3630.089	0.075188
PTGS2	24	0.17128217	3052.0334	0.074627
BCL2	21	0.2333712	1338.0535	0.075012
MAPK3	20	0.20237087	1391.0101	0.074731
JAK2	20	0.2176954	895.3119	0.073801
PIK3CA	20	0.19543669	1053.9296	0.073937
MTOR	19	0.1966216	687.53577	0.07428
MMP9	16	0.1849625	758.5622	0.074697
PLCG1	15	0.16433154	495.47272	0.073699
AR	13	0.116723545	817.9489	0.073869
MAPK14	13	0.1604464	445.23746	0.074246
PPARG	12	0.1304988	1487.9886	0.074453
NR3C1	12	0.1298642	745.6751	0.074246
PRKCA	11	0.09762376	857.81903	0.073597
PLA2G4A	11	0.07253661	369.63516	0.072431
FKBP5	11	0.09971498	426.24585	0.073227
CYP19A1	11	0.0691677	1125.1858	0.07286
CDK2	9	0.06309558	460.75174	0.072398
PPARA	9	0.05572784	2630.315	0.073835
GSK3B	9	0.07815179	914.92126	0.072694
KIT	9	0.10406542	491.32928	0.073193
NTRK1	6	0.047543466	1163.2194	0.072464
Average	5.838509	0.045256904	342.8447186	0.065725

4. KEGG Pathway Enrichment Analysis

KEGG pathway enrichment analysis was conducted using the ClueGO v2.5.10 plugin in Cytoscape. Pathways associated with the potential therapeutic mechanisms of *P. cocos* in epilepsy were selected based on statistically significant FDR values and included: “prostate cancer”, “lipid and atherosclerosis”, “vascular endothelial growth factor (VEGF) signaling pathway”, “receptor for advanced glycation end-products (AGE-RAGE) signaling pathway in diabetic complications” and “chemical carcinogenesis” (Table 3, Figure 3).

5. GO Biological Process Enrichment Analysis

GO Biological Process analysis was performed using ClueGO v2.5.10. Significant pathways with valid FDR values relevant to the therapeutic mechanism of P. cocos in epilepsy included: “regulation of blood vessel endothelial cell migration”, “blood vessel endothelial cell migration”, “positive regulation of lipid metabolic process”, “positive regulation of epithelial cell migration” and “phosphatidylinositol 3-kinase signaling” (Table 4, Figure 4).

Table 3. Top 5 KEGG Pathway Analysis of The Intersection Targets.

Category	FDR value	Term	Matched Genes	Background Genes	Gene Ratio	Associated Genes
KEGG Pathway	7.55×10^{-12}	Prostate cancer	10	97	10.31	[AKT1, AR, BCL2, CDK2, EGFR, GSK3B, MAPK3, MMP9, MTOR, PIK3CA]
	1.22×10^{-11}	Lipid and atherosclerosis	12	215	5.58	[AKT1, BCL2, GSK3B, JAK2, MAPK14, MAPK3, MMP9, PIK3CA, PLCG1, PPARG, PRKCA, TNF]
	1.13×10^{-10}	VEGF signaling pathway	8	59	13.56	[AKT1, MAPK14, MAPK3, PIK3CA, PLA2G4A, PLCG1, PRKCA, PTGS2]
	1.14×10^{-10}	AGE-RAGE signaling pathway in diabetic complications	9	100	9.0	[AKT1, BCL2, JAK2, MAPK14, MAPK3, PIK3CA, PLCG1, PRKCA, TNF]
	1.16×10^{-10}	Chemical carcinogenesis	11	212	5.19	[AKT1, AR, BCL2, EGFR, ESR1, JAK2, MAPK3, MTOR, PIK3CA, PPARA, PRKCA]

*KEGG, Kyoto Encyclopedia of Genes and Genomes; FDR, false discovery rate; AKT1, AKT serine/threonine kinase 1; AR, androgen receptor; BCL2, B-cell lymphoma 2; CDK2, cyclin-dependent kinase 2; EGFR, Epidermal growth factor receptor; GSK3B, glycogen synthase kinase 3 beta; MAPK3, mitogen-activated protein kinase 3; MMP9, matrix metallopeptidase 9; MTOR, mechanistic target of rapamycin; PIK3CA, phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha; JAK2, janus kinase 2; MAPK14, ; PLCG1, phospholipase C gamma 1; PPARG, peroxisome proliferator-activated receptor gamma; PRKCA, protein kinase C alpha; TNF, tumor necrosis factor; PLA2G4A, phospholipase A_2 group IVA; PTGS2, prostaglandin-endoperoxide synthase 2; ESR1, estrogen receptor 1; PPARA, peroxisome proliferator-activated receptor alpha

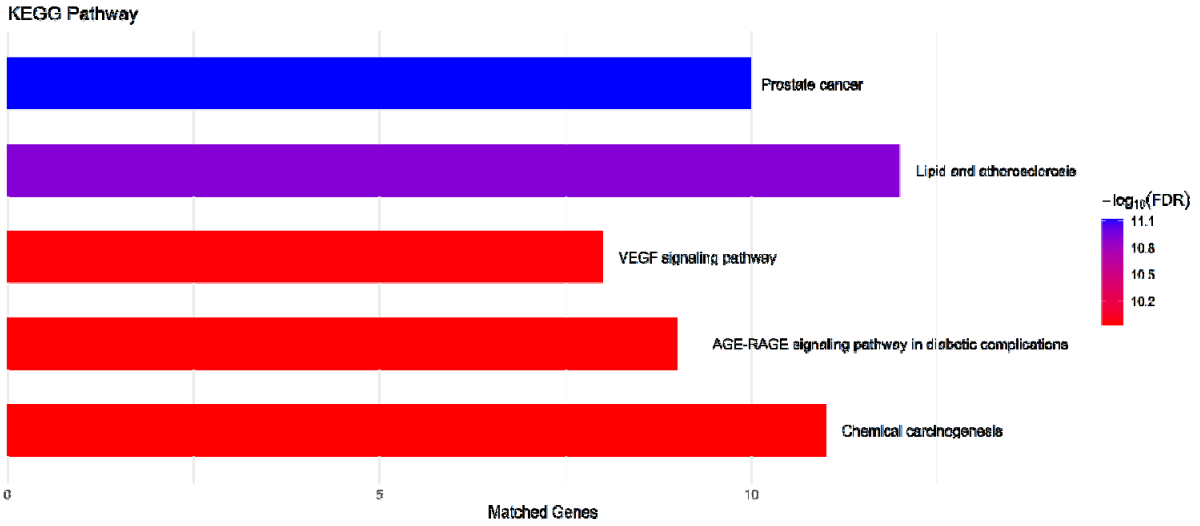

Figure 3. Kyoto encyclopedia of genes and genomes (KEGG) pathway analysis results of the intersection targets.

Table 4. Top 5 GO Biological Process Analysis of The Intersection Targets.

Category	FDR value	Term	Matched Genes	Background Genes	Gene Ratio	Associated Genes
GO Biological Process	4.69×10^{-09}	regulation of blood vessel endothelial cell migration	7	97	7.22	[AKT1, MAPK14, PLCG1, PPARG, PRKCA, PTGS2, TNF]
	1.42×10^{-08}	blood vessel endothelial cell migration	7	125	5.60	[AKT1, MAPK14, PLCG1, PPARG, PRKCA, PTGS2, TNF]
	2.50×10^{-08}	positive regulation of lipid metabolic process	7	165	4.24	[AKT1, KIT, MTOR, PPARA, PPARG, PTGS2, TNF]
	2.51×10^{-08}	positive regulation of epithelial cell migration	7	162	4.32	[AKT1, MAPK14, MMP9, MTOR, PLCG1, PRKCA, PTGS2]
	2.70×10^{-08}	phosphatidylinositol 3-kinase signaling	7	156	4.49	[AKT1, EGFR, JAK2, KIT, NTRK1, PIK3CA, TNF]

* GO, gene ontology; FDR, false discovery rate; AKT1, AKT serine/threonine kinase 1; MAPK14, Mitogen-activated protein kinase 14; PLCG1, phospholipase C gamma 1; PPARG, peroxisome proliferator-activated receptor gamma; PRKCA, protein kinase C alpha; PTGS2, prostaglandin-endoperoxide synthase 2; TNF, tumor necrosis factor; KIT, MTOR, mechanistic target of rapamycin; PPARA, peroxisome proliferator-activated receptor alpha; MMP9, matrix metallopeptidase 9; JAK2, Janus kinase 2; NTRK1, neurotrophic receptor tyrosine kinase 1

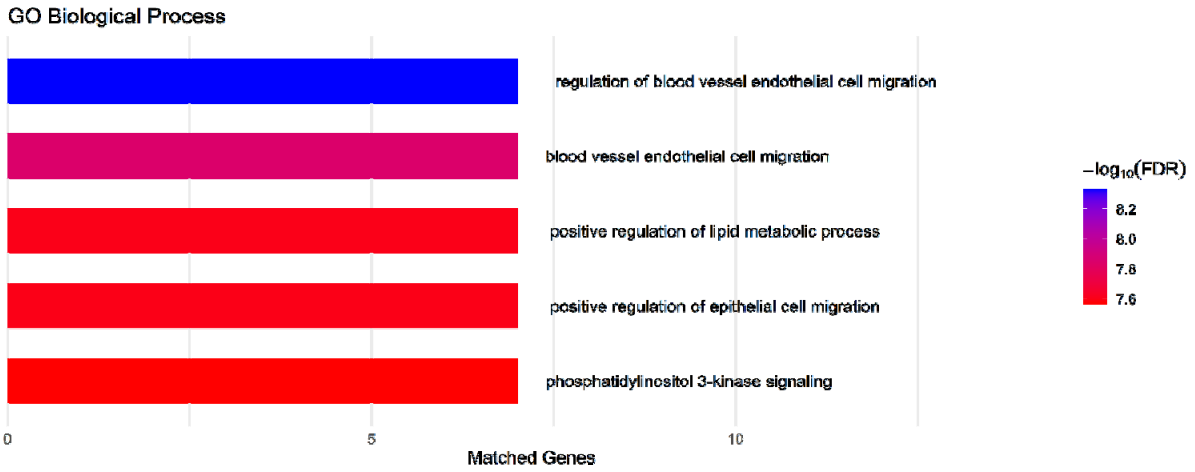

Figure 4. Gene ontology (GO) biological process analysis results of the intersection targets

6. GO Molecular Function Enrichment Analysis

In the GO Molecular Function analysis using ClueGO v2.5.10, the most relevant functions associated with the therapeutic effect of *P. cocos* on epilepsy were identified based on significant FDR values. These included: "ligand-activated transcription factor activity", "nuclear receptor activity", "nitric-oxide synthase regulator activity", "nitric-oxide synthase activity" and "protein serine/threonine/tyrosine kinase activity" (Table 5, Figure 5).

Table 5. Top 5 GO Molecular Function Analysis of The Intersection Targets.

Category	FDR value	Term	Matched Genes	Background Genes	Gene Ratio	Associated Genes
GO Molecular Function	4.02×10^{-07}	ligand-activated transcription factor activity	5	63	7.94	[AR, ESR1, NR3C1, PPARA, PPARG]
	4.02×10^{-07}	nuclear receptor activity	5	63	7.94	[AR, ESR1, NR3C1, PPARA, PPARG]
	7.71×10^{-07}	nitric-oxide synthase regulator activity	3	7	42.86	[AKT1, EGFR, ESR1]
	3.42×10^{-06}	nitric-oxide synthase activity	4	52	7.69	[AKT1, EGFR, ESR1, TNF]
	3.89×10^{-06}	protein serine/threonine/tyrosine kinase activity	4	50	8.0	[AKT1, MAPK14, MAPK3, PRKCA]

*GO, gene ontology; FDR, false discovery rate; AR, androgen receptor; ESR1, estrogen receptor 1; NR3C1, nuclear receptor subfamily 3 group C member 1; PPARA, peroxisome proliferator-activated receptor alpha; PPARG, peroxisome proliferator-activated receptor gamma; AKT1, AKT serine/threonine kinase 1; EGFR, epidermal growth factor receptor; TNF, tumor necrosis factor; MAPK14, mitogen-activated protein kinase 14; MAPK3, mitogen-activated protein kinase 3; PRKCA, protein kinase C alpha.

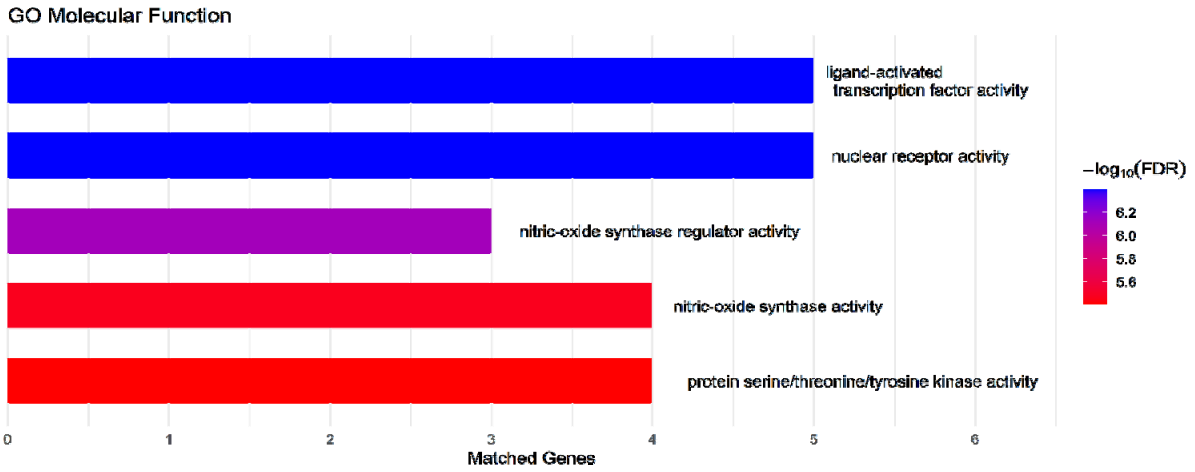

Figure 5. Gene ontology (GO) molecular process analysis results of the intersection targets.

Ⅳ. Discussion

1. Pharmacological relevance of *P. cocos* in epilepsy

Epilepsy is a neurological disorder characterized by chronic and recurrent seizures, often accompanied by neurological, cognitive, and social complications that significantly impair quality of life. Although various treatments, such as AEDs, dietary therapy, and surgical interventions, are currently available, approximately 30% of patients either do not respond adequately to existing therapies or experience side effects that limit their use. These limitations have led to increasing interest in the development of safer and more effective alternative treatments. In the field of traditional East Asian medicine, various herbal medicines have historically been utilized for the management of epilepsy. In recent years, *P. cocos* has gained attention for its potential anticonvulsant and neuroprotective effects. *P. cocos* contains various pharmacologically active constituents, primarily triterpenes and polysaccharides, which are of particular interest because of their potential to act simultaneously against multiple neurological targets[16]. *P. cocos* is a saprophytic fungus that grows near the roots of pine trees and forms large sclerotia that resemble potatoes. These sclerotia can reach up to 30 cm in length and weigh up to 1 kg. Its texture is soft and elastic, with a mildly sweet and bland taste. After harvest, *P. cocos* is typically dried in the shade before medicinal use. In traditional herbal medicine, it is classified based on anatomical regions, including Fu Ling Pi (茯苓皮, outer bark), Chi Fu Ling (赤茯苓, reddish outermost layer), Bai Fu Ling (白茯苓, white middle tissue), and Fu Shen (茯神, central core), each used according to its specific pharmacological properties. A recent updated meta-analysis of 30 randomized controlled trials demonstrated that traditional Chinese medicine, both as monotherapy and add-on therapy, significantly improved clinical efficacy and reduced adverse events in epilepsy treatment, with *P. cocos* identified as one of the five most frequently used herbs (appearing in 11 out of 26 traditional chinese medicine prescriptions)[7].

2. Core molecular targets and mechanisms

The PPI network constructed from the overlapping genes between *P. cocos* and epilepsy consisted of 161 nodes and 470 edges. Centrality analysis identified 25 core genes, including AKT serine/threonine kinase 1 (AKT1), mitogen-activated protein kinase 3 (MAPK3), epidermal growth factor receptor (EGFR), tumor necrosis factor (TNF), and B-cell lymphoma 2 (BCL2). These genes are involved in key pathways related to cell survival, neuroinflammatory responses, synaptic plasticity, and programmed cell death.

AKT1, a central component of the phosphatidylinositol 3-kinase (PI3K) downstream signaling pathway, plays a pivotal role in the pathogenesis and progression of epilepsy[17]. It regulates astrocyte response and survival following status epilepticus (SE). The inhibition of AKT after SE has been shown to reduce Poly (ADP-Ribose) Polymerase 1 activity in the Cornu Ammonis 1 region of the hippocampus, thereby suppressing reactive astrocyte proliferation and increasing cell death. Conversely, in the dentate gyrus, AKT inhibition exacerbates astrocyte loss, whereas its activation promotes cell survival, suggesting a region-specific role for AKT in astrocyte biology. Moreover, AKT modulates phosphorylation of proliferation and apoptosis adaptor protein 15 (PEA15) and Nuclear factor kappa B (NF-κB), key regulators of astrocyte survival and apoptosis. In particular, changes in PEA15-S116 and NF-κB phosphorylation are closely associated with astrocyte reactivity and viability[18].

MAPK3 is a component of the mitogen-activated protein kinase (MAPK) cascade and is involved in the translation of local proteins during epileptogenesis. The activation of the ERK pathway promotes eIF4E phosphorylation, which increases the expression of NR2B, thereby enhancing N-methyl-d-aspartate (NMDA) receptor activity and seizure susceptibility. Additionally, both mammalian target of rapamycin (mTOR) and MAPK pathways regulate RNA-binding proteins, leading to localized expression of epilepsy-related proteins[19].

TNF-α is a key mediator of neuroinflammation associated with epilepsy. Recurrent seizures or SE trigger activation of microglia and astrocytes, resulting in the upre-

gulation of proinflammatory cytokines such as TNF-α, interleukin 1β (IL-1β), and interleukin 6 (IL-6)[20]. These cytokines contribute to seizure generation and progression by increasing neuronal excitability, altering synaptic plasticity. TNF-α, in particular, modulates gene expression through cross-talk with the NF-κB signaling pathway and is also involved in trafficking of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and GABA receptors[21].

Prostaglandin-endoperoxide synthase 2 (PTGS2) encodes cyclooxygenase-2 (COX-2) and catalyzes the rate-limiting step in prostaglandin (PG) biosynthesis[22]. COX-2 induces the synthesis of various PGs and endocannabinoid metabolites that activate inflammatory cascades. Seizures markedly upregulate COX-2 expression in the hippocampus and cerebral cortex, resulting in increased levels of Prostaglandin E_2 (PGE_2) and Prostaglandin D_2 (PGD_2), which further amplify neuroinflammation, excitotoxicity, and neuronal damage[23]. Among these, PGE_2 has been shown to contribute to epileptogenesis through the Prostaglandin E receptor 1 (EP1) and Prostaglandin E receptor 2 (EP2) receptors. The antagonism of EP1 receptors delays seizure onset[24], whereas the inhibition of EP2 receptors attenuates inflammation, preserves blood–brain barrier (BBB) integrity, and exerts neuroprotective effects[25].

BCL2 encodes a major anti-apoptotic protein that regulates neuronal cell death, a key event in the pathogenesis of epilepsy. Seizure-induced neuronal loss involves both excitotoxic necrosis and programmed apoptosis in which members of the *BCL2* gene family play central roles. BCL2 family proteins influence the initiation and progression of apoptosis by regulating the mitochondrial outer membrane permeability[26]. Altered expression of BCL2 family members has been observed in the hippocampus and neocortex of patients with drug-resistant temporal lobe epilepsy.

3. Key signaling pathways

The key biological mechanisms identified through functional enrichment analysis helped specify the pharmacological scope of *P. cocos*. Based on the FDR values, the top five signaling pathways were selected from the KEGG analysis: Prostate cancer, Lipid and atherosclerosis, VEGF signaling pathway, AGE-RAGE signaling pathway in diabetic complications, and Chemical carcinogenesis. These findings suggest that the active components of *P. cocos* modulate a wide range of mechanisms relevant to the pathophysiology of epilepsy, including neuronal survival, inflammation, and vascular stability.

The 10.31% gene overlap between *P. cocos* targets and the Prostate Cancer Pathway is notable, prompting closer examination of shared underlying mechanisms. Key genes within this pathway—*EGFR, MAPK3, PIK3CA, AKT1*, and *mTOR*—are well-established mediators in both cancer progression and various aspects of epilepsy pathogenesis. The PI3K–AKT–mTOR axis plays a critical role in the regulation of neuronal growth, survival, and inflammatory responses. Although hyperactivation of this pathway in prostate cancer is often associated with treatment resistance, it is essential for maintaining cellular homeostasis[27]. In epilepsy, mTOR hyperactivation can contribute to seizure development; however, its appropriate activation supports neuroprotection and synaptic plasticity[28]. This putative molecular overlap is indirectly supported by clinical observations. For instance, a Finnish prostate cancer cohort study found that valproic acid users had a 38% lower relative risk of prostate cancer (OR 0.62, 95% CI 0.42–0.92), and carbamazepine users showed an 18% reduction (OR 0.82, 95% CI 0.71–0.94)[29]. Therefore, our findings are best interpreted as a generating a mechanistic hypothesis that *P. cocos* may exert its neuroprotective effects through modulation of these shared upstream signaling nodes. However, the direct link between *P. cocos* targest, these cancer-related pathways, and actual anticonvulsant efficacy requires definitive experimental validation in cell and animal models. Lipid and atherosclerotic pathways are also relevant, as recent studies in animal models of temporal lobe epilepsy (TLE) animal models have shown upregulation of cholesteryl esters and downregulation of fatty acids, indicating that lipid metabolic imbalance may play a direct role in epileptogenesis[30]. The VEGF signaling pathway is activated following epileptic seizures, promoting hippocampal neural stem cell proliferation. VEGF exerts neuroprotective ef-

fects during the acute phase, and contributes to ectopic neuronal migration and angiogenesis during the latent phase[31]. In immature brains, particularly in lithium–pilocarpine–induced SE models, VEGF supports cognitive recovery by regulating neurogenesis. In particular, the vascular endothelial growth factor receptor 2 (VEGFR2) pathway controls Neural stem cell proliferation and migration[32]. VEGF may also reduce the severity of spontaneous recurrent seizures by activating the ERK and AKT pathways[33]. The AGE–RAGE signaling pathway in diabetic complications is involved in neuroinflammatory responses and drug resistance in epilepsy. Advanced glycation end-products (AGEs) activate RAGE and TLR4 via HMGB1, leading to P-glycoprotein overexpression in brain endothelial cells, thereby increasing drug resistance. RAGE signaling is upregulated in TLE and contributes to experimental seizure generation, whereas inhibition of this pathway elevates seizure thresholds and significantly reduces the frequency of chronic spontaneous seizures[34].

GO Biological Process analysis identified five major: Regulation of blood vessel endothelial cell migration, Blood vessel endothelial cell migration, Positive regulation of lipid metabolic process, Positive regulation of epithelial cell migration, and Phosphatidylinositol 3-kinase signaling.

The regulation of blood vessel endothelial cell migration plays a pivotal role in maintaining vascular stability and BBB integrity in epilepsy. In the neocortical microvasculature of patients with epilepsy, increased expression of VEGF-A and VEGFR-2 is accompanied by the downregulation of tight junction proteins such as occludin and Zonula occludens-1 (ZO-1), promoting endothelial cell migration while impairing BBB function[35]. This highlights the dual role of VEGF signaling in enhancing endothelial motility and vascular permeability. Proinflammatory cytokines also significantly influence endothelial cell migration. In an endothelial-specific IL-1R1 knockout mouse model, IL-1R1 signaling modulates hippocampal neuroinflammation and seizure susceptibility via the Nuclear factor erythroid 2–related factor 2 (Nrf2)/Heme oxygenase-1 (HO-1)/NOD-like receptor family pyrin domain containing 3 (NLRP3) axis[36]. The VEGFR-2 inhibitor sunitinib significantly reduced angiogenesis and seizure occurrence in pilocarpine-induced seizure models[37], whereas rapamycin, an mTOR inhibitor, suppresses the positive feedback loop of VEGF signaling, thereby alleviating BBB disruption and microglial activation[38]. These findings support the therapeutic potential of targeting endothelial migration in epilepsy pathophysiology and suggest that the blood vessel endothelial cell migration pathway is also central to the pathological angiogenesis observed in epilepsy. Increased vascular density has been reported in the hippocampal tissue of patients with drug-resistant temporal lobe epilepsy, positively correlating with seizure frequency, regardless of the etiology or degree of neuronal loss. In particular, the dentate gyrus shows abnormal radial microvascular structures in areas with granule cell dispersion, reflecting the characteristic vascular pathology in epilepsy[39]. VEGF contributes to BBB breakdown through a dual mechanism involving VEGFR-2/Src-mediated ZO-1 suppression and E26 transformation-specific sequence 1–induced synthesis of matrix metallopeptidase 2/9 (MMP2/MMP9), which degrades ZO-1 and further increase permeability[40]. By modulating these pathways, *P. cocos* may attenuate pathological angiogenesis, restore BBB function, and normalize the neurovascular unit, thereby contributing to disease-modifying effects in epilepsy. Furthermore, PI3K signaling is closely linked to epilepsy pathogenesis. In neuron-specific phosphatase and tensin homolog (PTEN) knockout mice, isoform-selective PI3K inhibition restores molecular defects and reduces epilepsy-related phenotypes[41]. Dual targeting of the PI3K/Akt/mTOR pathway has been shown to alleviate seizure-induced neuroinflammation and related neurodegeneration[42]. Additionally, studies have reported that hippocampal PIP3 levels decrease after seizures, and valproic acid treatment restores these levels[43]. These findings underscore the central role of PI3K signaling in regulating neuronal excitability and cell survival, suggesting that *P. cocos* may exert therapeutic effects by modulating this pathway.

In the GO Molecular Function analysis, the top five enriched pathways were identified as 'ligand-activated transcription factor activity', 'nuclear receptor activity', 'nitric-oxide synthase regulator activity', 'nitric-oxide synthase activity', and 'protein serine/threonine/tyrosine kin-

ase activity'.

'Ligand-activated transcription factor activity' plays a pivotal role in the transcriptional regulation associated with epilepsy. Among the proline and acidic amino acid-rich basic leucine zipper (PAR bZIP) family of transcription factors, hepatic leukemia factor is consistently downregulated in acquired epilepsy models, a change linked to neuronal excitability regulation[44]. The dysregulation of various transcription factors, including the activator protein 1 (AP-1) complex, drives aberrant gene expression patterns in drug-resistant TLE[45]. 'Nuclear receptor activity' is closely related to hormonal signaling pathways in epilepsy. Nuclear receptor (NR) 4A1, a downstream target of cyclic adenosine monophosphate (cAMP) response element-binding protein, acts as a key modulator in epileptogenesis. Inhibition of NR4A1 has been reported to reduce seizure severity and prolong seizure latency. Mechanistically, NR4A1 interacts with N-methyl-D-aspartate receptor type 2B (NR2B) to regulate the surface expression of NMDA receptors, thereby modulating neuronal excitability and seizure susceptibility[46]. 'Nitric oxide synthase (NOS) activity' exhibits dual roles in epilepsy pathophysiology. Neuronal NOS (nNOS) contributes to excitotoxicity and cell death in various neurodegenerative conditions. Suppression of nNOS activity has been shown to raise seizure thresholds, suggesting an anticonvulsant effect. The nNOS/reactive oxygen species axis has been implicated in both apoptotic and pyroptotic neuronal death in epilepsy models[47]. Conversely, endogenous nitric oxide has also been reported to facilitate seizure initiation in the hippocampus and entorhinal cortex, highlighting its complex involvement in epileptic networks[48]. 'Protein serine/threonine/tyrosine kinase activity' governs various intracellular signaling cascades relevant to seizure pathogenesis. Protein kinase C plays a context-dependent role in epilepsy, whereas protein kinase A activation during the late phase of status epilepticus enhances the phosphorylation of the AMPA receptor GluR1 subunit, influencing synaptic excitability[49].

4. Limitations and clinical implications

This study integrated previously reported bioactive compounds and target gene data of *P. cocos* using a network pharmacology-based approach to predict its potential multi-component, multi-target mechanisms in pediatric epilepsy. This methodological framework offers a novel means of elucidating the complex pharmacological actions of herbal medicines, offering preliminary insights supporting the epilepsy-related biological networks of P.cocos. However, this study has some limitations inherent to in silico network pharmacology. The predicted associations between *P. cocos* and epilepsy-related targets are based solely on existing databases and do not confirm actual pharmacological or clinical efficacy. Moreover, factors such as compound bioavailability, blood–brain barrier permeability, and pharmacokinetic stability were not considered. Therefore, these results should be interpreted as hypothesis-generating, and additional in vitro and in vivo studies are required to validate the proposed molecular mechanisms and therapeutic implications. Future studies should focus on validating the key targets and pathways identified through network analysis, investigating compound–compound interactions, and characterizing dose-dependent effects to establish a more robust therapeutic basis.

Ⅴ. Conclusion

This study systematically explored the potential molecular mechanisms by which *P. cocos* may influence the pathophysiology of pediatric epilepsy using a network pharmacology approach. These findings highlight several multicomponent, multitarget, and multi-pathway properties:

1. Network analysis of 11 major active compounds of *P. cocos* revealed that 175 of the 241 predicted targets overlapped with epilepsy-related genes, indicating a substantial biological overlap that may provide a hypothesis-generating basis for potential clinical relevance.

2. PPI analysis identified 25 core genes, including *AKT1, MAPK3, EGFR, TNF*, and *BCL2*, that are involved in key pathophysiological processes in epilepsy, such as cell survival, neuroinflammation regulation, synaptic plasticity, and apoptosis.

3. Functional enrichment analysis further demonstrated that *P. cocos* may modulate diverse biological pathways, including VEGF signaling, PI3K pathway, regulation of vascular endothelial cell migration, lipid metabolic processes, transcription factor activity, and protein kinase activity.

Notably, these findings propose plausible molecular pathways through which *P. cocos* could interact with epilepsy-related biological networks. However, as this study was based on a database-driven predictive analysis, the results should be interpreted as exploratory and hypothesis-generating rather than indicative of confirmed therapeutic efficacy. Future research should focus on the experimental verification of the core targets and pathways identified in this study and the evaluation of compound-compound interactions, dose-response relationships, and age-specific responses in pediatric populations.

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Appendix 1. 241 Target Proteins of *Poria Cocos*.

ABL1, ACE, ACHE, ACP1, ADORA1, ADORA2A, ADORA3, AGTR1, AKR1B10, AKR1C2, AKR1C3, AKT1, ALK, ALOX12, ALOX15, ALOX5, ALOX5AP, AMPD3, AR, AURKA, AURKAIP1, AURKB, AVPR1A, AVPR2, BACE1, BACE2, BCHE, BCL2, CALCRL, CASR, CCKBR, CCND1 CDK4, CCNE2 CDK2 CCNE1, CCNT1, CCR1, CD81, CDC25A, CDC25B, CDC25C, CDC7, CDK2, CDK8, CES1, CES2, CHRM1, CHRM2, CHUK, CNR1, CNR2, CPB1, CSF1R, CTRC, CTSD, CYP17A1, CYP19A1, CYP2C19, CYP51A1, CYSLTR1, DGAT1, DRD2, EDNRA, EDNRB, EGFR, ENPP2, EPAS1, ESR1, ESR2, F10, F11, F2, FAAH, FABP1, FABP3, FABP4, FABP5, FDFT1, FFAR1, FFAR2, FKBP1A, FKBP4, FKBP5, FNTA FNTB, G6PD, GCGR, GPBAR1, GRIA2, GRIN2A GRIN1, GRM1, GRM2, GRM5, GSK3B, GYS1, HAO1, HCRTR1, HCRTR2, HMGCR, HSD11B1, HSD11B2, HSD17B2, HSD17B3, HTR6, IDO1, IKBKB, IMPDH1, IMPDH2, ITGA2B ITGB3, ITGA4, ITGAL ICAM1 ITGB2, ITGAV ITGB3, ITGB1 ITGA4, ITGB5 ITGAV, ITGB7 ITGA4, JAK1, JAK2, JAK3, KCNA3, KCNA5, KDR, KIT, LRRK2, LTB4R, MAP3K14, MAPK10, MAPK14, MAPK3, MAPK8, MDM2, MDM4, MET, MGLL, MIF, MME, MMEL1, MMP1, MMP10, MMP12, MMP13, MMP2, MMP3, MMP7, MMP8, MMP9, MTNR1A, MTNR1B, MTOR, NLRP3, NOS2, NPC1L1, NR1H2, NR1H3, NR1H4, NR1I2, NR1I3, NR3C1, NR3C2, NTRK1, NTSR1, OPRD1, OPRK1, OPRL1, OPRM1, OXTR, PDE10A, PDE2A, PDE4B, PDE4D, PDGFRB, PFKFB3, PGR, PIK3CA, PIN1, PLA2G1B, PLA2G4A, PLCG1, PLEC, POLB, PPARA, PPARD, PPARG, PREP, PRKCA, PRKCB, PRKCE, PRKCH, PRSS1, PSEN2 PSENEN NCSTN APH1A PSEN1 APH1B, PTGDR, PTGDR2, PTGER1, PTGER2, PTGER3, PTGER4, PTGES, PTGFR, PTGIR, PTGS1, PTGS2, PTPN1, PTPN11, PTPN2, PTPN6, PTPRF, PYGL, RASGRP3, ROCK1, ROCK2, RORA, RORC, S1PR1, S1PR2, S1PR3, SAE1 UBA2, SCD, SERPINA6, SGK1, SHBG, SIGMAR1, SLC10A1, SLC10A2, SLC22A6, SLC6A2, SLC6A3, SLC6A4, SMO, SRD5A2, SREBF2, TACR1, TACR2, TBXA2R, TBXAS1, TERT, THRA, THRB, TLR9, TNF, TOP1, TOP2A, TRPM8, TRPV1, TYMS, VDR