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Research Article

Exploring Mechanism of Pelargonidin in Treatment of Pediatric Pneumonia Based on Network Pharmacology Combined with Molecular Docking

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Abstract

Background and Objective: Pediatric pneumonia is a common and potentially serious respiratory infection. In this study, the network pharmacology combined with molecular docking analysis was used to investigate the common molecular mechanism of pelargonidin (PG) in the treatment of pediatric pneumonia. **Materials and Methods:** The disease-related targets were found out from the GeneCards, DisGeNET and DigSee databases. The target genes of PG were screened through HIT platform. Then, the protein-protein interaction (PPI) network was built by STRING database to identify core-hub targets of PG acting on pediatric pneumonia. Next, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis were employed to analyze the protein effects and enriched regulatory pathways of the PG in pediatric pneumonia. Lastly, molecular docking analysis were further verifying the interaction between the key targets and PG. **Results:** A total of 22 pneumonia-related target proteins of PG from the relevant databases were screened out. Among these target proteins, EIF4EBP1, RPTOR, EIF4E, RICTOR, TSC2, NCOA3 and SP1 were core-hub genes in PPI network. The GO analysis and KEGG pathway enrichment analysis indicated that the targets might regulate the PI3K-Akt, mTOR and thyroid hormone signaling pathways. Additionally, EIF4E and RICTOR were the most promising candidates from the results of molecular docking. **Conclusion:** The present study for the first time identified that the potential targets (EIF4E and RICTOR) of PG in pediatric pneumonia mainly involved in the PI3K-Akt signaling pathway, thereby providing a basis for further understanding of PG in clinical treatments.

Key words: Pelargonidin, pediatric pneumonia, network pharmacology, EIF4E, RICTOR, PI3K-Akt signal pathway

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Pediatric pneumonia is a form of common acute respiratory infection that affects the lungs, which makes breathing painful and limits oxygen intake. Pneumonia is a common and potentially serious respiratory infection in children[1], characterized by various complications including multiorgan failure, parapneumonic effusion, bacteremia, acute respiratory distress syndrome, lung abscess and even death[2]. In 2019, pneumonia induced 740,180 death in children under age of five, which occupying 14% of all children deaths and 22% of 1-5 year-old deaths[3]. Prompt diagnosis and appropriate treatment are highly needed to prevent complications and reduce the mortality of pediatric pneumonia. First-line and preferred agent for pediatric pneumonia treatment is antibiotics such as amoxicillin, cephalosporins, macrolide antibiotics and quinolones. However, the increasing resistance to antibiotics due to multi-drug resistance pathogens and mild or serious side effects like childhood tendonitis/tendinopathy, stomach upset and allergic reactions limit the development of antibiotics in treatment for pediatric pneumonia[4]. Due to the challenge in clinical prevention and treatment in pneumonia, it is necessary to explore new therapies for pediatric pneumonia[5].

Traditional Chinese medicine (TCM) exhibits various advantages in treatment of pediatric pneumonia, such as multi-component-multi-target-multi-pathway and less side effects[6]. The TCM can also improve symptoms and eliminate vital infections in patients with pediatric pneumonia[7]. Chinese herbal medicines have shown promise for the treatment of pneumonia such as Sha-Shen-Mai-Dong decoction, Liujunzi decoction, Danshen injection and Yupingfeng granules[8]. Pelargonidin (PG) is an anthocyanidin, which is a type of plant metabolite, displaying diverse bioactivities[9]. Moreover, PG has been demonstrated to possess multiple health benefits including anti-cancer, improvement of neurodegenerative diseases, anti-inflammation, anti-oxidant, anti-diabetic and bacteriostatic activities[10]. The PG shows an important anti-inflammatory property which is mainly involved in the effect on Mitogen-Activated Protein Kinases (MAPK), nuclear transcript factors NF-κB and AP-1[11]. The therapeutic properties of PG in treatment of pediatric pneumonia have not been elucidated. Therefore, our study was aimed to clarify the biological mechanism of PG acting on pediatric pneumonia to provide a novel clinical treatment.

Network pharmacology provides a useful tool for studying the biological systems of TCM. It is a promising method to identify the relationships between drugs, targets and diseases based on computational pharmacology from existed research results, such as drug-target interaction and disease networks[12]. Molecular docking is a computational method that investigates the interactions of the protein-ligand, drug and selected targets[13]. Molecular docking and network pharmacology can be combined to explore the mechanism of action of TCM and identify the bioactive components and potential targets[14]. Xu *et al.*[15] identified the bioactive ingredients of Yinlai decoction (YD) and the possible targets and mechanism of these ingredients in treating pneumonia by network pharmacology combined with molecular docking. The YD is verified to treat LPS-induced pneumonia by regulating the inflammatory factor IL-6[15]. To investigate the active ingredients and potential targets of Xie Bai San (XBS) in treating pediatric pneumonia, 120 active ingredients of XBS and 128 potential targets are screened out by a network pharmacology approach[16]. Kim and Kim[17] found that PG could improve the influenza-induced inflammation and boost the immune system with influenza treatment by network pharmacology analysis. Therefore, network pharmacology integrated with molecular docking helps to effectively obtain the possible targets and pathways of PG in the treatment of pediatric pneumonia.

In this study, a network pharmacologic analysis was performed to explore the potential mechanism of PG against pediatric pneumonia. Disease-related targets, drug targets and the potential protein targets of PG were obtained from various databases. The protein-protein interaction (PPI) network was also constructed to find out the core genes. On this basis, further screening and validation of protein targets were performed by molecule docking. Current research investigated the mechanism of PG and provided a potent foundation for the clinical use of PG for treating pediatric pneumonia.

MATERIALS AND METHODS

Study area: The study is conducted in Department of Pharmacy, Shulan (Hangzhou) Hospital Affiliated to Zhejiang Shuren University Shulan International Medical College, Hangzhou, China, in April, 2023.

Selection of disease-related targets: The Genecards[18], DisGeNET[19] and DigSee[20] databases were utilized to obtain disease-related targets by using “pediatric pneumonia”, “infantile pneumonia”, “child pneumonia”, “pneumonia in children” and “pneumonia childhood” as the key words.

Next, the results of the disease targets were integrated and the duplicated genes were deleted.

Screening of PG targets: In HIT database[21,22], the keyword "Pelargonidin" was used to search for PG targets. Additionally, target genes were retrieved from SEA and Super-PRED databases[23] according to the simplified molecular input line entry specification (SMILES) structure of PG. Finally, a screened genes and deleted duplicates were merged.

Identification of PG targets in pediatric pneumonia: To determine the common targets of PG targets and pediatric pneumonia targets, the identified "PG targets" and "disease targets" were mapped using the Venn diagram 1.7.3 software[24].

Construction of PPI network: The PPI plays a significant role in the biological processes under physiological conditions[25]. To better visualize the drug-target-disease interaction, the STRING platform was used to build PPI network[26]. The target genes were screened according to the condition of score_cutoff >0.4 and size_cutoff <40. The target genes with high degree in the network were screened out and were likely key targets of PG acting on pediatric pneumonia. Then, we utilized the Cytoscape to construct the PPI network and core genes were further identified. In order to find the core genes, MNC, MCC, EPC and DMNC algorithms in cytoHubba[27] were utilized to compute the core genes. Finally, the intersection of the core genes screened by four algorithms was selected via Venn diagram.

GO and pathway enrichment analyses: The tool of clusterProfiler 4.4.2 was used for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis of genes in PPI networks[28]. The principle of enrichment analysis is to apply the hypergeometric distribution model to evaluate whether target gene sets are significantly associated with specific gene ontology and biological pathways by the following equation:

$$P = 1 - \sum_{i=0}^{K-1} \frac{\binom{M}{i}\binom{N-M}{n-i}}{\binom{N}{n}}$$

where, N is the total number of genes and M is the number of annotated genes in a pathway or GO. The n is the input target gene and k is the number of the common genes. The p-value calculated through statistical test reflects the intensity of the association between input target genes and the pathway or GO. The p-values <0.05 were considered as statistically significant.

Analysis of molecular docking: Molecular docking aims to verify the binding mode between the selected core genes and PG. The RCSB protein database[29] was used to download the structure of the target proteins and the mol2 format file for PG structure was obtained from ZINC[30]. Next, the downloaded protein and drug files were converted into PDBQT format by Babel GUI software. Additionally, Pymol and Autodock1.5.6 were then used to optimize the structure of protein including removal of original ligands and water, addition of hydrogen and amino acids and charge calculation[31]. Finally, Autodock1.5.6 was used for molecular docking and Pymol was for visualization the docking results.

RESULTS

Collection of target genes for PG in treating pediatric pneumonia: After eliminating the overlaps, 496 disease-related targets genes were obtained from the Genecards, DisGeNET and DigSee databases. Moreover, a total of 124 PG targets were obtained from HIT, SEA and Super-PRED databases. As a result, a total of 22 combined targets were obtained by Venn diagram 1.7.3 (Fig. 1) and detailed information of 22 common targets for PG treating pediatric pneumonia was exhibited in Table 1.

Fabrication of PPI network: The STRING database was used to predict the interaction of 22 target proteins and the PPI network was shown in Fig. 2. In order to find the core genes in PPI network, the core targets were identified by MNC, MCC, EPC and DMNC algorithms, as illustrated in Fig. 3a. The common core genes selected by various algorithms were identified by Venn diagram (Fig. 3b), including EIF4EBP1, RPTOR, Eukaryotic Initiation Factor 4E (EIF4E), RICTOR, TSC2, NCOA3 and SP1.

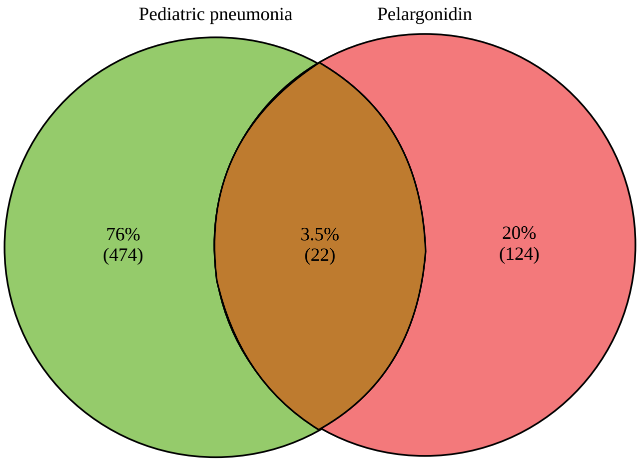


Fig. 1: Venn diagram of drug and disease proteins

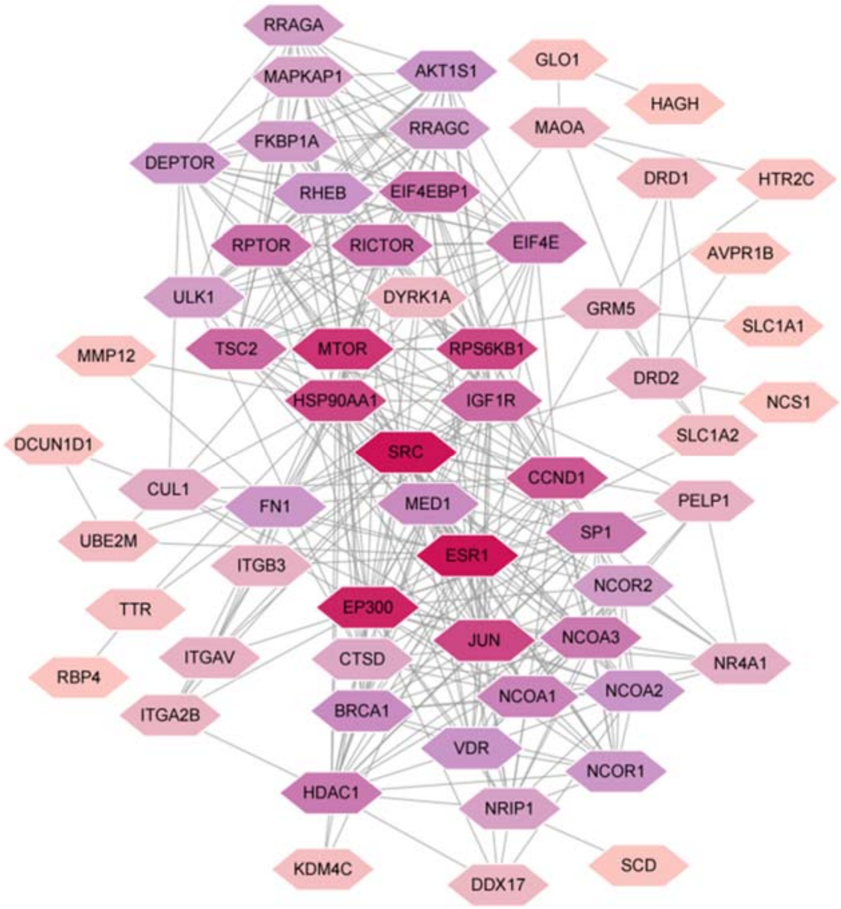


Fig. 2: Fabrication of protein-protein interaction (PPI) network of pelargonidin (PG) in pediatric pneumonia
Color shade of the node is proportional to its degree

Table 1: Twenty two targets of pelargonidin (PG) treating pediatric pneumonia

Gene name	Gene name
GLO1	DYRK1A
DRD2	VDR
SLC1A2	GRM5
SLC1A1	CTSD
HTR2C	NR4A1
KDM4C	SCD
MAOA	GLRA1
ITGB3	AVPR1B
MTOR	ESR1
DCUN1D1	MMP12
DRD1	TTR

Table 2: Free energy information of pelargonidin (PG) with core target molecules

Compound	Target	Free binding energy (kcal/mol)
PG	EIF4E	-8.5
	RICTOR	-7.1

GO and pathway enrichment analyses: In the GO analysis, the targets were involved in 64 molecular function (MF), 661 biological process (BP) and 54 cellular component (CC) terms. The top 15 categories were displayed in Fig. 4a and Table S1. Target genes may be involved in response to steroid hormone (BP), transcription regulator complex (CC) and DNA-binding

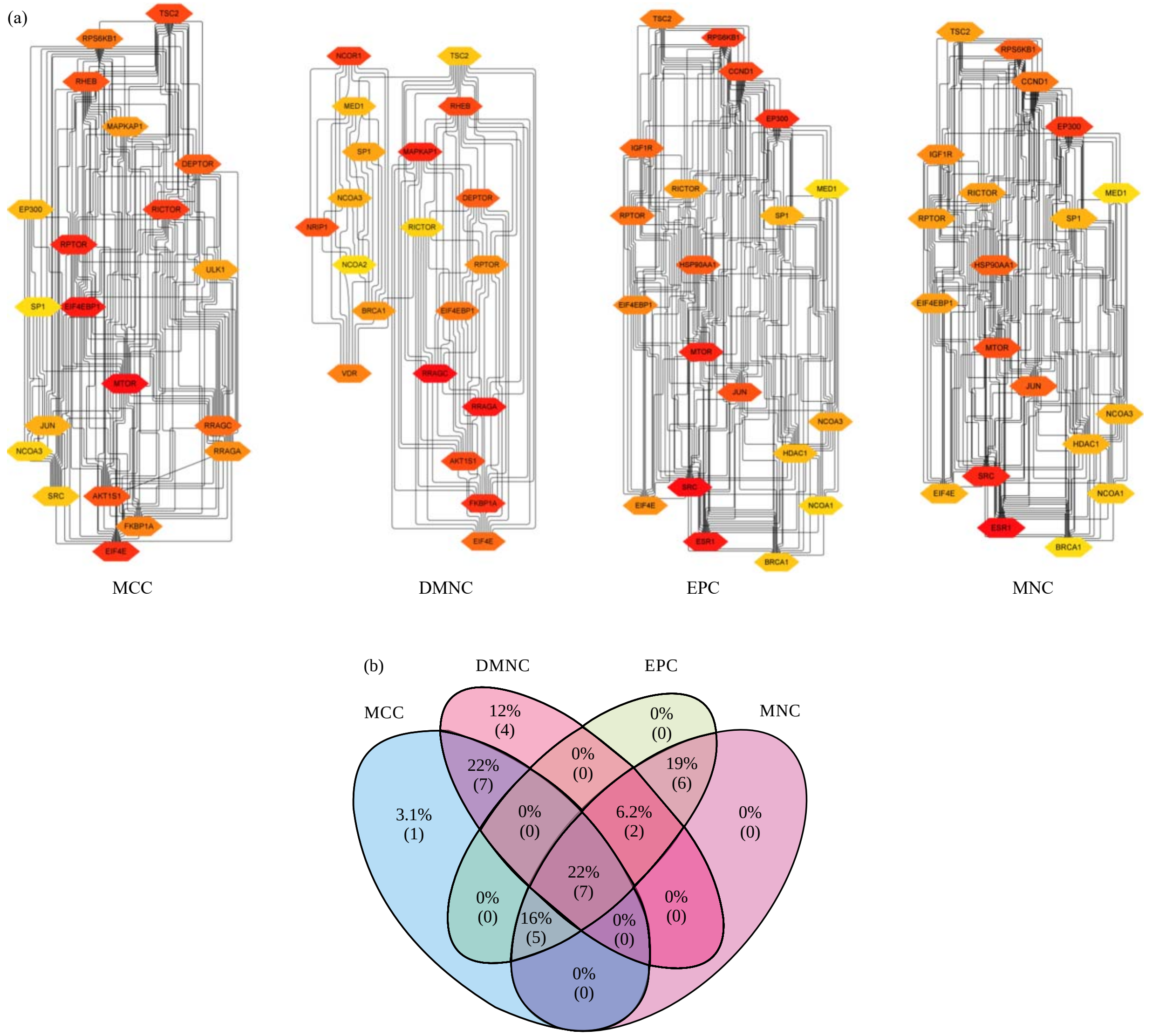


Fig. 3(a-b): Identification of hub-genes in the protein-protein interaction (PPI) network, (a) Hub-genes were screened by four algorithms in PPI network and (b) Venn diagram of hub-gene intersection screened by four algorithms in PPI network

transcription factor binding (MF). In the pathway enrichment analysis, there were 71 associated pathways and the top15 pathways were exhibited in Fig. 4b and Table S2. The PG might act on pediatric pneumonia by these regulatory pathways including PI3K-Akt, thyroid hormone and mTOR signaling pathways. Additionally, the core genes in PPI network were mainly involved in mTOR, AMPK and PI3K-Akt signaling pathways, as shown in Fig. 5.

Molecular docking: The binding energy of targets and PG was less than-5.0 kcal/mol and hydrogen bonds could be formed between receptor ligands and PG as the screening criteria. The analysis (Table 2 and Fig. 6a-d) found that the binding affinity between the PG and EIF4E was-8.5 kcal/mol and the binding energy between the PG and RICTOR was -7.1 kcal/mol. The EIF4E and RICTOR were the putative target genes which had stable binds with PG, while other candidate targets could not form the stable hydrogen bond with PG.

DISCUSSION

Pediatric pneumonia is a form of acute respiratory infection that affects the lungs[32] and is one of the largest infectious cause of death in children worldwide[33]. Current immunization prevention and antibiotic therapy are applied

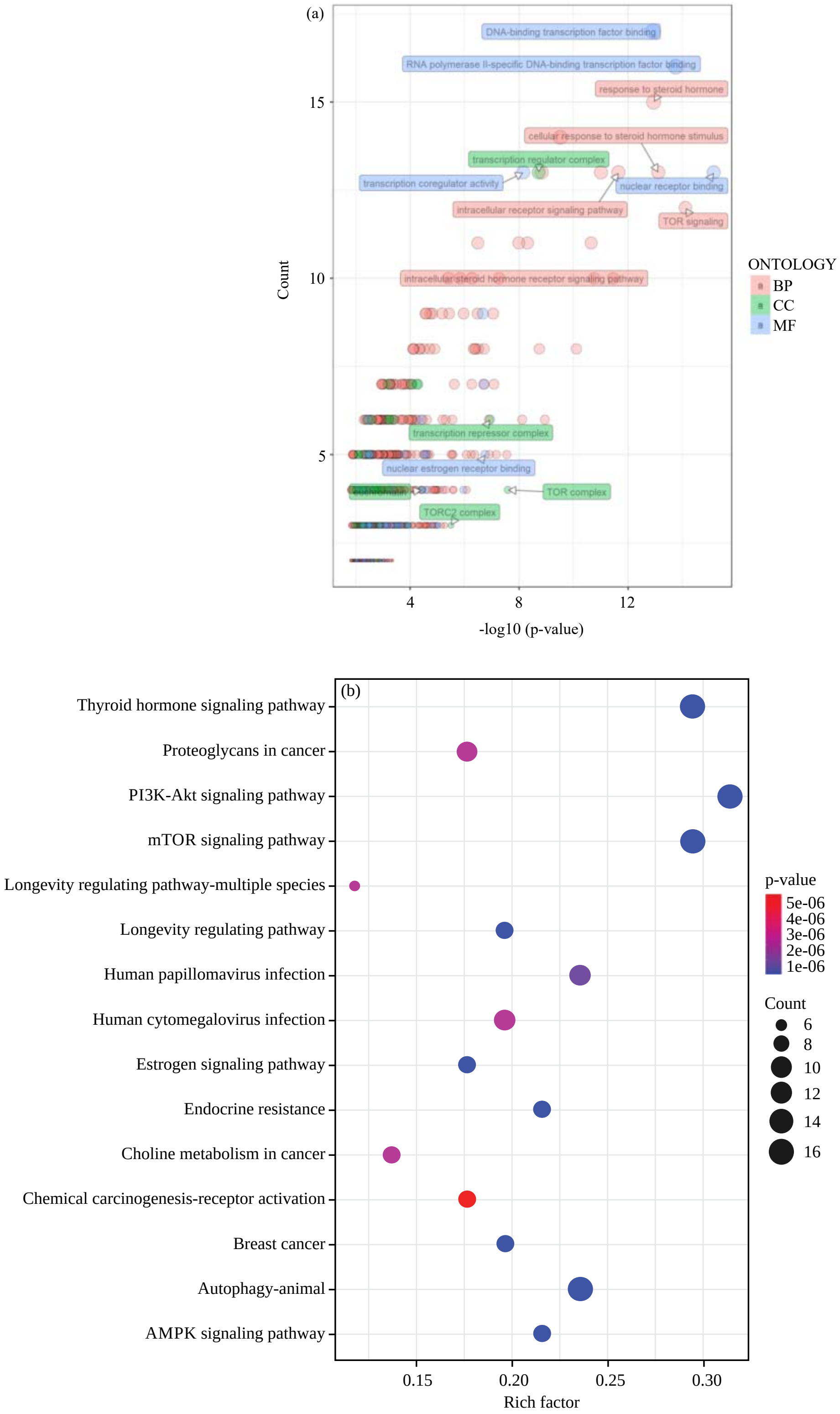


Fig. 4(a-b): Gene ontology (GO) and pathway enrichment analysis of the targets for pelargonidin (PG) acting on pediatric pneumonia. The 15, (a) Most significance of GO and (b) Pathway enrichment, analyses of therapeutic target genes of PG in pediatric pneumonia

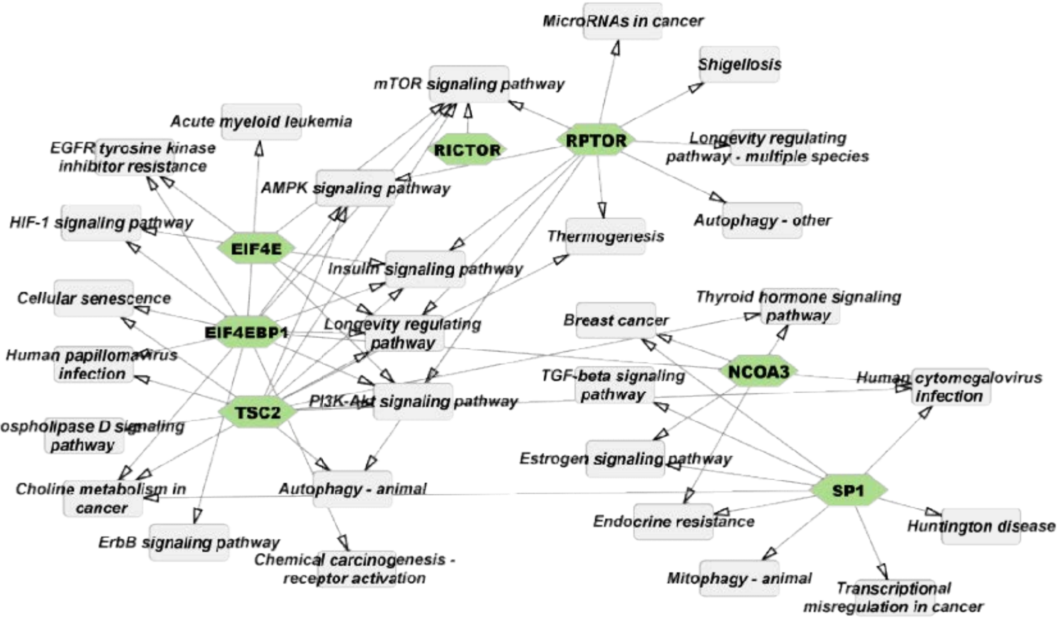
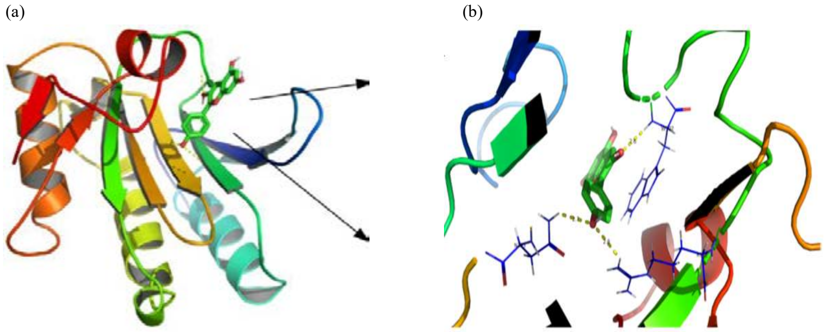
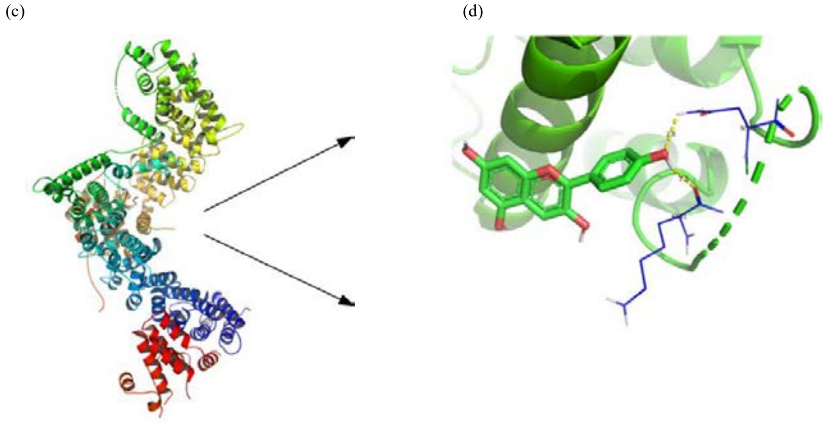


Fig. 5: Signaling pathway analysis of core genes of pelargonidin (PG) in pediatric pneumonia



EIF4E

Binding site



RICTOR

Binding site

Fig. 6(a-d): Molecular docking of pelargonidin (PG) with (a) EIF4E molecule, (b) Bind site, results of the docking of PG with (c) RICTOR molecule and (d) Bind site to protect against infection sources, but the persistent mortality from pneumonia remains high. It is urgent to search for more effective treatments to lessen this persistent mortality of pneumonia. The PG, a type of anthocyanin, is a naturally plant compound exhibiting antioxidant activity[34], anti-inflammatory effects and anti-tumor activity[35]. The PG also showed bacteriostatic effects as natural preservatives agents[36]. Moreover, PG could reduce the inflammatory reactions by inhibiting cytokinins and histamines. Winter *et al.*[37]. found that PG could inhibit the expression of inflammatory factors and reduce the production of inflammatory substances in rats. Furthermore, PG exerts the anti-inflammatory effects for treating the colitis in mice[38]. Xu *et al.*[39] verified that the anti-inflammatory effects were related to an NF-κB mechanism. However, little study has been made on the potential therapeutic effects of PG to alleviate the course of pediatric pneumonia and pharmacological effects have not been reviewed. It has been suggested that pneumonia is one of the common respiratory tract inflammatory diseases[40]. The pathological mechanism of pneumonia is complex, which is related to the adhesion injury, toxin injury, immune theory and micro-circulation disorder.

In this work, network pharmacology approach integrated with molecular docking was successfully used to demonstrate the potential targets and mechanism of PG against pediatric pneumonia. Bioinformatics analysis revealed that the 22 targets of PG were related to the action on pediatric pneumonia. Molecular docking is a computational technique commonly used to identify potential targets that can interact with PG[41]. Remarkably, EIF4E and RICTOR showed the strong binding affinity with PG in our molecular docking results, indicating that these two targets are essential for PG against pediatric pneumonia. The EIF4E, a potential target for transcriptional control, could regulate the activity of upstream effect kinases including Akt, PI3K and mTOR[42]. The EIF4E function plays a critical role in various physiological processes including mRNA translation, protein synthesis, cellular growth and differentiation. Some EIF4E specific siRNA could inhibit cell growth in cancer, squamous carcinoma and adenocarcinoma[43]. The EIF4E is also indirectly targeted by inhibitors of the mTOR pathway[44]. Moreover, another target RICTOR plays a role in regulation of pro-inflammatory cytokines by the NF-κB pathway which is related to the effect of anti-pneumonia. Additionally, RICTOR could activate NF-κB which is downstream of mTOR and render cell apoptosis. RICTOR is also considered as a key regulator of the PI3K-AKT pathway and participates in tumor growth, invasion and drug resistance[45].

In this study, EIF4E and RICTOR exhibited a high affinity to bind with PG, showing that PG could regulate inflammation and cell apoptosis to treat pediatric pneumonia.

The EIF4E and RICTOR targets of PG were mainly involved in the regulation of inflammation-related pathways including mTOR, AMPK and PI3K-Akt signaling pathway which were characterized as the important mechanism of anti-pneumonia. The PI3K/Akt/mTOR pathway is a signaling pathway that regulates several cellular processes, including cell survival, proliferation, regulation of cell cycle, angiogenesis and metabolism. Additionally, the PI3K/Akt pathway mediates extracellular and intracellular signaling to maintain the function of immune system and regulate inflammatory response[46]. The regulation of dysfunctional immune system and inflammatory response is beneficial to the treatment of pneumonia. The activated PI3K/Akt signaling pathway plays a significant role in anti-inflammatory property, antioxidant stress, anti-apoptosis and autophagy regulation by acting on downstream pathways and proteins. The PI3K can inhibit the activation of NF-κB and its downstream pro-inflammatory cytokines. Additionally, PI3K alleviates the inflammatory response in pneumonia by inactivating TLR4 signaling[47]. The PI3K/Akt signaling pathway is inhibited to up-regulate the release of pro-inflammatory cytokines like TNF-α, IL-1β and IL-6 to ultimately exacerbate pneumonia[48]. Moreover, mTOR is a downstream effector of the PI3K/AKT pathway, which regulates the cell growth, proliferation and survival[49]. Furthermore, the PI3K/Akt signaling pathway is a classical anti-apoptotic pathway which could regulate caspase 3-mediated cell death. The activation of the PI3K/Akt/mTOR signaling pathway protect cells from apoptosis and significantly improve pneumonia[50]. The action of PG in anti-pneumonia is also involved in AMPK signaling pathway, an evolutionarily conserved sensor of cellular energy status, which could inhibit the NF-κB pathway to regulate inflammation and immune responses[51]. Current network pharmacology analysis for the regulatory effect of PG were mainly on the anti-inflammation signaling pathway. According to the above results, PG might exert its anti-pneumonia by targeting EIF4E and RICTOR genes which is involved in PI3K-Akt, AMPK and mTOR signaling pathways.

CONCLUSION

To sum up, the pharmacological mechanism of PG acting on pediatric pneumonia was predicted by network pharmacology and molecular docking. The PG can act on multiple therapeutic targets to treat pediatric pneumonia.

Current results demonstrated that EIF4E and RICTOR are core targets of PG in pediatric pneumonia. The PI3K-Akt, AMPK and mTOR signaling pathways may be the key pathways of PG acting on the pediatric pneumonia. These findings further suggested that the promising clinical application of PG in pediatric pneumonia, but more experiments are demanded to verify the molecular mechanism of PG action.

SIGNIFICANCE STATEMENT

In the present study, the network pharmacology combined with molecular docking analysis was performed to investigate the common molecular mechanism of pelargonidin in the treatment of pediatric pneumonia. The study for the first time identified that the potential targets (EIF4E and RICTOR) of PG in pediatric pneumonia mainly involved in the PI3K-Akt signaling pathway, thereby providing a basis for further understanding of PG in clinical treatments.

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Table S1: First 15 gene ontology analysis of pelargonidin (PG) targets

Ontology	ID	Description	p-value	Gene ID	Count
BP	GO:0031929	TOR signaling	7.70E-15	TSC2/RPS6KB1/RHEB/MAPKAP1/DEPTOR/RICTOR/RPTOR/EIF4EBP1/MTOR/RRAGC/RRAGA/AKT1S1	12
BP	GO:0071383	Cellular response to steroid hormone stimulus	7.68E-14	RPS6KB1/EP300/IGF1R/NCOR1/MED1/HDAC1/SRC/KDM4C/DDX17/NCOR2/ESR1/BRCA1/EIF4E	13
BP	GO:0048545	Response to steroid hormone	1.15E-13	RPS6KB1/CCND1/EP300/IGF1R/NCOR1/MED1/HDAC1/SRC/KDM4C/DDX17/NCOR2/NCOA2/ESR1/BRCA1/EIF4E	15
BP	GO:0030522	Intracellular receptor signaling pathway	2.22E-12	EP300/NCOR1/MED1/HDAC1/SRC/KDM4C/DDX17/NCOR2/NCOA1/ESR1/BRCA1/VDR/NR4A1	13
BP	GO:0030518	Intracellular steroid hormone receptor signaling pathway	3.42E-12	EP300/NCOR1/MED1/HDAC1/SRC/KDM4C/DDX17/NCOR2/ESR1/BRCA1	10
CC	GO:0005667	transcription regulator complex	1.90E-09	CCND1/EP300/NCOR1/MED1/SP1/JUN/HDAC1/NCOR2/NCOA1/NCOA2/ESR1/VDR/NR4A1	13
CC	GO:0038201	TOR complex	2.58E-08	MAPKAP1/RICTOR/RPTOR/MTOR	4
CC	GO:0017053	Transcription repressor complex	1.18E-07	CCND1/NCOR1/SP1/JUN/HDAC1/NCOR2	6
CC	GO:0031932	TORC2 complex	3.23E-06	MAPKAP1/RICTOR/MTOR	3
CC	GO:0000791	euchromatin	3.88E-05	PELP1/SP1/JUN/ESR1	4
MF	GO:0016922	Nuclear receptor binding	7.05E-16	EP300/NCOR1/MED1/NCOA3/SRC/KDM4C/NRIP1/NCOR2/NCOA1/NCOA2/ESR1/VDR/NR4A1	13
MF	GO:0061629	RNA polymerase II-specific DNA-binding transcription factor binding	1.77E-14	EP300/NCOR1/MED1/SP1/JUN/NCOA3/HDAC1/SRC/KDM4C/NRIP1/NCOR2/NCOA1/NCOA2/ESR1/VDR/NR4A1	16
MF	GO:0140297	DNA-binding transcription factor binding	1.19E-13	EP300/NCOR1/MED1/SP1/JUN/NCOA3/HDAC1/SRC/KDM4C/NRIP1/NCOR2/NCOA1/NCOA2/ESR1/EIF4E/VDR/NR4A1	17
MF	GO:0003712	Transcription coregulator activity	6.96E-09	CCND1/EP300/NCOR1/MED1/NCOA3/HDAC1/DDX17/DYRK1A /NRIP1/NCOR2/NCOA1/NCOA2/BRCA1	13
MF	GO:0030331	nuclear estrogen receptor binding	1.78E-07	MED1/SRC/NRIP1/NCOA1/ESR1	5

Table S2: First 15 signaling pathways of pelargonidin (PG) targets

ID	Description	p-value	Gene ID	Count
hsa04919	Thyroid hormone signaling pathway	3.16E-16	TSC2/CCND1/ITGAV/RHEB/EP300/NCOR1/MED1/MTOR/NCOA3/HDAC1/SRC/NCOA1/NCOA2/ESR1/ITGB3	15
hsa04150	mTOR signaling pathway	1.52E-14	TSC2/RPS6KB1/RHEB/MAPKAP1/IGF1R/DEPTOR/RICTOR/RPTOR/ULK1/EIF4EBP1/MTOR/RRAGC/RRAGA/AKT1S1/EIF4E RPS6KB1/CCND1/	15
hsa01522	Endocrine resistance	1.37E-11	IGF1R/NCOR1/MED1/SP1/MTOR/JUN/NCOA3/SRC/ESR1	11
hsa04140	Autophagy-animal	4.01E-11	TSC2/RPS6KB1/CTSD/RHEB/IGF1R/DEPTOR/RPTOR/ULK1/MTOR/RRAGC/RRAGA/AKT1S1	12
hsa04211	Longevity regulating pathway	1.28E-10	TSC2/RPS6KB1/RHEB/IGF1R/RPTOR/ULK1/EIF4EBP1/MTOR/AKT1S1/EIF4E	10
hsa04152	AMPK signaling pathway	1.29E-10	TSC2/RPS6KB1/CCND1/RHEB/IGF1R/RPTOR/ULK1/EIF4EBP1/MTOR/SCD/AKT1S1	11
hsa04151	PI3K-Akt signaling pathway	2.06E-10	TSC2/RPS6KB1/CCND1/ITGAV/RHEB/ITGA2B/IGF1R/RPTOR/HSP90AA1/EIF4EBP1/FN1/MTOR/BRCA1/EIF4E/ITGB3/NR4A1	16
hsa05224	Breast cancer	1.82E-08	RPS6KB1/CCND1/IGF1R/SP1/MTOR/JUN/NCOA3/NCOA1/ESR1/BRCA1	10
hsa04915	Estrogen signaling pathway	1.47E-07	CTSD/SP1/HSP90AA1/JUN/NCOA3/SRC/NCOA1/NCOA2/ESR1	9
hsa05165	Human papillomavirus infection	6.29E-07	TSC2/RPS6KB1/CCND1/ITGAV/RHEB/ITGA2B/EP300/EIF4EBP1/FN1/MTOR/HDAC1/ITGB3	12
hsa05163	Human cytomegalovirus infection	9.99E-07	TSC2/RPS6KB1/CCND1/ITGAV/RHEB/SP1/EIF4EBP1/MTOR/SRC/ITGB3	10
hsa04213	Longevity regulating pathway-multiple species	2.09E-06	RPS6KB1/IGF1R/RPTOR/MTOR/HDAC1/AKT1S1	6
hsa05231	Choline metabolism in cancer	2.20E-06	TSC2/RPS6KB1/RHEB/SP1/EIF4EBP1/MTOR/JUN	7
hsa05205	Proteoglycans in cancer	4.12E-06	RPS6KB1/CCND1/ITGAV/IGF1R/FN1/MTOR/SRC/ESR1/ITGB3	9