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Screening and mechanism analysis of core target genes for resveratrol inhibiting respiratory syncytial virus

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Abstract: **Background**: Respiratory syncytial virus (RSV), a single-stranded negative-sense RNA virus, is a major pathogen of acute respiratory tract infections, posing severe threats to the health of infants, the elderly and immunocompromised individuals. While approved vaccines for older adults and monoclonal antibody prophylaxis for infants are available, effective therapeutic drugs remain scarce. Resveratrol, a phenolic compound naturally present in grapes, berries and other foods, has been confirmed to exhibit anti-RSV activity, but its molecular mechanism of action remains unclear. **Objectives**: This study aimed to screen the core targets and key signaling pathways of resveratrol against RSV using computational biology approaches, propose testable research hypotheses and provide a theoretical basis for subsequent experimental validation. **Methods**: A total of 261 resveratrol-related targets and 1196 RSV-related targets were retrieved from databases. Venny 2.1.0 was used to identify 67 overlapping targets, which were then subjected to protein-protein interaction (PPI) network construction via STRING/Cytoscape and topological analysis for core target screening. GO/KEGG enrichment analyses were performed using the DAVID database and molecular docking validation was conducted with PyMOL/AutoDock. **Results**: Ten core targets including EGFR, SRC, HSP90AA1 and ALB were identified. GO enrichment focused on biological processes such as PI3K-Akt signal transduction and MAPK cascade regulation, while KEGG pathways were enriched in the Ras signaling pathway and others. Molecular docking showed stable binding of resveratrol to core targets, with all binding energies <-5 kcal/mol. **Conclusion**: This *in-silico* study predicts that resveratrol may exert anti-RSV effects by targeting host proteins such as EGFR and SRC and regulating key pathways including PI3K-Akt and Ras, complementing existing evidence of its direct interaction with viral proteins. The study provides novel insights for anti-RSV drug development and a theoretical foundation for subsequent experimental validation.

Keywords: Core targets; Molecular docking; Network pharmacology; Resveratrol; Respiratory syncytial virus (RSV)

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INTRODUCTION

Respiratory syncytial virus (RSV) belongs to the *Pneumoviridae* family and *Orthopneumovirus* genus, which is a negative-sense single-stranded RNA virus that causes epidemics of respiratory infections (Duan *et al.*, 2024). RSV infection is a persistent public health problem, especially among infants and the elderly. Almost all children are infected with RSV before the age of two and recurrent infections throughout life are common (Agac *et al.*, 2023). RSV is capable of inducing acute upper and lower respiratory tract infections, which are occasionally associated with extrapulmonary complications and also serves as a major contributor to morbidity and mortality among children, elderly individuals and immunocompromised patients (Duan *et al.*, 2024; Zhang *et al.*, 2024). Despite the significant impact of RSV on global human health, progress has been made in preventive interventions; three vaccines (Arexvy, Abrysvo and mRESVIA) have been approved worldwide for active immunization in adults aged 60 years and older and pregnant women, while the monoclonal antibody nirsevimab is licensed for RSV prophylaxis in infants (Liang *et al.*, 2025). However, effective antiviral treatments for post-infection cases remain limited—currently, no widely recommended specific therapeutics are available for clinical use (Oppenlander *et al.*, 2023), as inhaled ribavirin is no longer advised due to its nonspecific mechanism, potential genotoxicity and uncertain efficacy (Liang *et al.*, 2025). Therefore, developing effective anti-RSV therapeutic drugs possesses significant clinical value.

Being a phenolic constituent with abundant presence in grapes, wine, peanuts and berries, resveratrol has been a focus of interest among scientists and physicians for decades (Faisal *et al.*, 2024). Extensive research has indicated that resveratrol exhibits diverse biological activities, encompassing antioxidant, anti-inflammatory, cardiovascular protection, anti-diabetic, anti-obesity, neuroprotective and anti-aging effects (Zhou *et al.*, 2021). Resveratrol also has anti-cancer effects, including against breast cancer, hepatic cancer, lung cancer, etc (Ren *et al.*, 2021). In addition, resveratrol has been demonstrated to exert notable antiviral effects against a broad spectrum of viruses responsible for severe respiratory tract infections (Leonardi *et al.*, 2025). It was found that resveratrol can potently suppress RSV infection in a dose-dependent fashion through its interaction with SPGs (Xiong *et al.,*

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2024). A group of researchers prepared highly soluble resveratrol nanoparticles (Res NPs) and demonstrated that these nanoparticles exert antiviral activity by impeding RSV replication and diminishing the secretion of pro-inflammatory cytokines (Chang *et al.,* 2024). Resveratrol has been experimentally shown to inhibit RSV replication by directly binding to the viral matrix (M) protein (Rodrigues *et al.*, 2024).

However, these studies primarily focus on viral components and lack systematic exploration of host-derived targets and regulatory pathways. RSV infection relies heavily on host cell machinery (e.g., signal transduction, protein folding, immune response) and deciphering host-level targets can uncover multi-dimensional mechanisms of resveratrol's action that single viral protein-focused experiments cannot address. To fill this gap, network pharmacology and molecular docking were integrated to identify the core host targets of resveratrol and their associated pathways, thereby providing a comprehensive understanding of its anti-RSV effect.

Centered on systems biology, network pharmacology can precisely forecast the potential targets and pathways through which drugs exert therapeutic effects on diseases via multi-pathway regulatory signal transduction cascades, thereby furnishing crucial technical backing for in-depth investigations into drug mechanisms (Liu *et al.*, 2022; Noor *et al.*, 2023). Molecular docking technology serves as a critical tool in drug discovery and development, given its ability to simulate binding interactions between small-molecule ligands and target proteins, while simultaneously forecasting the most favorable binding conformation and minimum free energy when the two form a stable complex (Aguiar and Camps, 2025).

This study innovatively combines network pharmacology and molecular docking to explore the antiviral mechanism of resveratrol against respiratory syncytial virus (RSV). A dual-mechanism hypothesis involving "viral protein interference plus host pathway regulation" is proposed herein, which complements existing experimental evidence and provides a comprehensive theoretical framework for the development of antiviral drugs.

MATERIALS AND METHODS

Study design

The current study adopted a comprehensive research method combining database mining, network analysis and molecular simulation, with the aim of systematically exploring the potential targets and the mechanism through which resveratrol exerts anti-RSV effects. The technical route included target screening, intersection target identification, PPI network construction, functional enrichment analysis and molecular docking verification.

Screening of resveratrol targets

The 2D structure of resveratrol was sourced from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and the SMILES number was saved. To determine its potential targets, the Swiss Target Prediction database (http://www.swisstargetprediction.ch/)(Daina and Zoete, 2024) and PharmMapper database (http://www.lilab-ecust.cn/pharmmapper/) (Wang *et al.*, 2017) were applied for predictive analysis. Invalid and duplicate targets were excluded to identify potential resveratrol targets.

Screening of RSV-related targets

The keyword "respiratory syncytial virus" was adopted to perform targeted searches in the GeneCards database (https://www.genecards.org) (Stelzer *et al.*, 2016; Tian *et al.*, 2024) and the OMIM database (https://www.omim.org) (Amberger and Hamosh, 2017; Wang *et al.*, 2022). Indirect or disease-unrelated targets were excluded and high-confidence candidate targets were retained. Duplicate target records were removed to screen out potential RSV-associated targets.

Identification of intersection targets

The candidate targets of resveratrol and the predicted targets associated with RSV were separately submitted to the Venny 2.1.0 platform (https://bioinfogp.cnb.csic.es/tools/venny/). After undergoing targeted screening, the intersecting targets of the two datasets were obtained and a corresponding Venn diagram was plotted.

PPI network construction and analysis

The intersection targets shared by resveratrol and RSV were input into the STRING database (https://string-db.org) (Szklarczyk *et al.*, 2019); subsequently, the "*Homo sapiens*" classification was selected for subsequent analysis, and the threshold for the minimum interaction score was configured at 0.7. Results exported in TSV format were uploaded to Cytoscape 3.9.1 software for network topological assessment (Doncheva *et al.*, 2023), from which the degree value of every target was derived; the top 10 core targets were subsequently pinpointed via targeted screening.

Functional enrichment analysis based on GO and pathway analysis via KEGG

The overlapping targets of resveratrol and RSV were submitted to the DAVID database (https://david.ncifcrf.gov/) (Sherman *et al.*, 2022)for the purpose of conducting GO functional enrichment and KEGG pathway enrichment analyses. The organism was specified as "*Homo sapiens*", and with $P < 0.05$ set as the screening cutoff, the top 10 entries for each of the GO function subcategories (biological process [BP], cellular component [CC] and molecular function [MF]), as well as the top 10 pathways derived from KEGG enrichment analysis. GO functional bar charts and KEGG enrichment bubble charts were generated after visualization.

Molecular docking

The 3D structure of resveratrol was acquired by downloading it from the PubChem database (https://pubchem.ncbi.nlm.nih.gov). The PDB files of core targets were obtained from the PDB database (https://www.rcsb.org). Pymol (Seeliger and de Groot, 2010) and Autodock software (Trott and Olson, 2010) were used to dehydrate, de-ligand, add hydrogen and electrons to the receptor proteins. The obtained core targets were docked with resveratrol respectively and then imported into PyMOL for visualization.

RESULTS

Acquisition of resveratrol targets

Target screening was performed in the Swiss Target Prediction and PharmMapper databases, and redundant records were subsequently merged to ultimately obtain 261 potential action targets of resveratrol (Fig. 1).

Acquisition of intersection targets

Target screening in the GeneCards and OMIM databases, combined with the removal and merging of duplicate entries, yielded a total of 1196 targets associated with RSV. Subsequently, targets linked to resveratrol and RSV were uploaded to the Venny 2.1.0 tool, which yielded 67 overlapping targets and a corresponding Venn diagram was generated for visualization (Fig. 2).

Establishment of PPI network and screening of core targets

The overlapping targets associated with the inhibitory effect of resveratrol on RSV were uploaded to the STRING database, and the analytical parameters were then adjusted by selecting "*Homo sapiens*" as the target species and fixing the minimum confidence threshold at 0.7. Data results were exported and formatted as "tsv" files for subsequent analysis. Cytoscape 3.9.1 software was employed to create visualizations of the PPI network (Fig. 3). Topological analysis was conducted via Cytohubba with the degree value of each node as the criterion, and the top 10 targets ranked by degree were identified as epidermal growth factor receptor (EGFR), non-receptor tyrosine kinase (SRC), heat shock protein 90α family class A member 1 (HSP90AA1), albumin (ALB), matrix metalloproteinase 9 (MMP9), cysteinyl aspartate-specific proteinase 3 (CASP3), prostaglandin-endoperoxide synthase 2 (PTGS2), mitogen-activated protein kinase 1 (MAPK1), mitogen-activated protein kinase 8 (MAPK8) and insulin-like growth factor 1 (IGF1) (Fig. 4).

GO functional enrichment analysis

GO enrichment analysis results showed that 337 biological processes (BP), 49 cellular components (CC) and 101 molecular functions (MF) were obtained in total. Among them, biological processes (BP) were primarily associated with pivotal biological events, which included positive regulation of phosphatidylinositol 3-kinase/protein kinase B signal transduction, insulin-like growth factor receptor signaling pathway, epidermal growth factor receptor signaling pathway, cellular response to lipopolysaccharide, positive regulation of MAPK cascade, signal transduction and response to external stimuli; cellular components (CC) mainly consisted of subcellular structures such as extracellular region, extracellular space, cytoplasm, ficolin-1-rich granule lumen, receptor complex, extracellular vesicles and collagen-containing extracellular matrix; molecular functions (MF) primarily encompassed molecular functions such as peptidase activity, enzyme binding, histone H2AXY142 kinase activity, protein tyrosine kinase activity, histone H3Y41 kinase activity, endopeptidase activity, ATP binding and insulin receptor binding (Fig. 5).

Functional enrichment analysis of KEGG pathways

Data derived from KEGG enrichment analysis indicated that 147 signaling pathways were successfully enriched, encompassing cancer-related pathways, lipid and atherosclerosis, proteoglycans in cancer, relaxin signaling pathway, fluid shear stress and atherosclerosis, prostate cancer, endocrine resistance, Ras signaling pathway, phagosome death and AGE signaling pathway involved in diabetic complications. The top 10 pathways exhibiting the lowest P values were chosen to create a bubble chart (Fig. 6).

Molecular docking results

Molecular docking assays were performed between resveratrol and the core targets EGFR, SRC, HSP90AA1 and ALB respectively. The molecular docking outcomes demonstrated that resveratrol possessed favorable binding energy with the core targets and all of the corresponding docking binding energies were lower than -5 kcal/mol. The binding energies of resveratrol with the above targets were -8.4, -6.4, -6.8 and -8.8 kcal/mol, respectively (Table 1, Fig. 7). Molecular docking results provide computational supportive evidence for the potential stable binding of resveratrol to the predicted core targets, reflecting the potential binding affinity and structural compatibility between resveratrol and target proteins under simulated *in-vitro* conditions.

DISCUSSION

Respiratory syncytial virus (RSV) is a primary contributor to respiratory tract infections across the globe, leading to roughly 3 million hospital admissions and over 100,000 fatalities annually among children under 5 years of age, imposing a significant global medical burden (Zhang *et al.*, 2024). There is a pressing requirement for novel therapeutic agents and universal prevention strategies to prevent RSV infection.

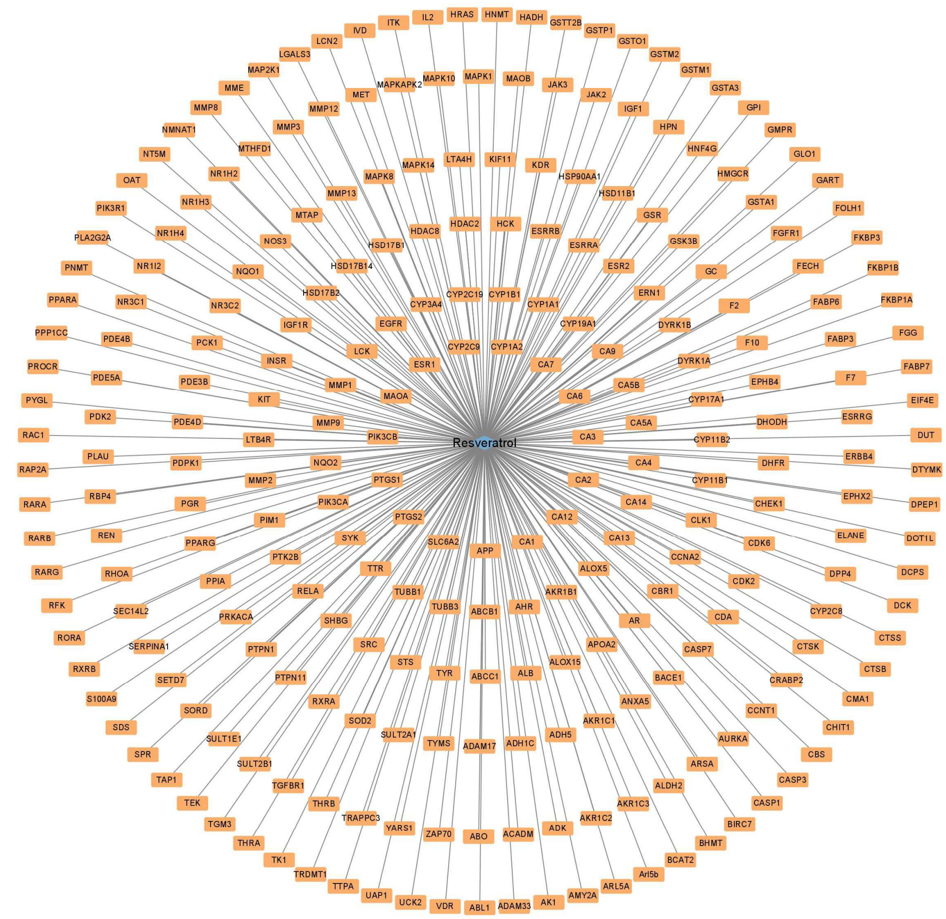

Fig. 1: Network diagram of resveratrol drug targets.

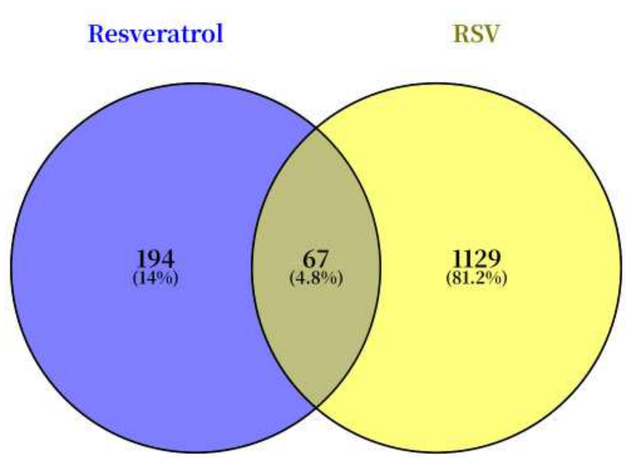

Fig. 2: Venn diagram of intersection targets of resveratrol against RSV.

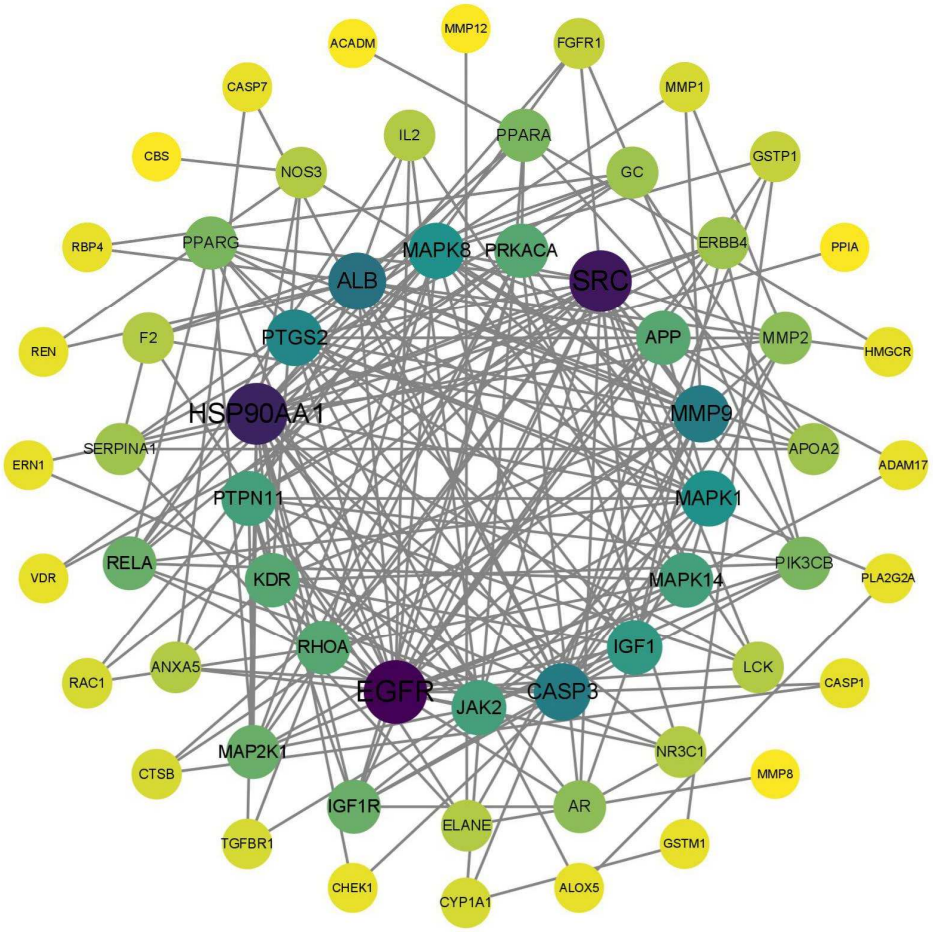

Fig. 3: PPI network of potential targets of resveratrol against RSV.

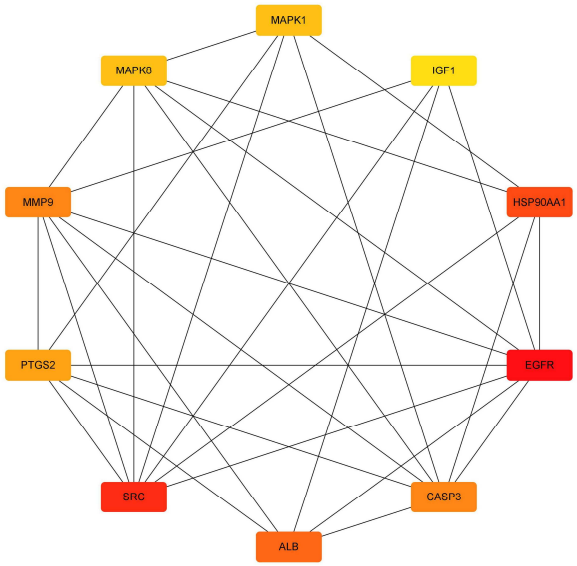

Fig. 4: PPI network of core targets of resveratrol against RSV.

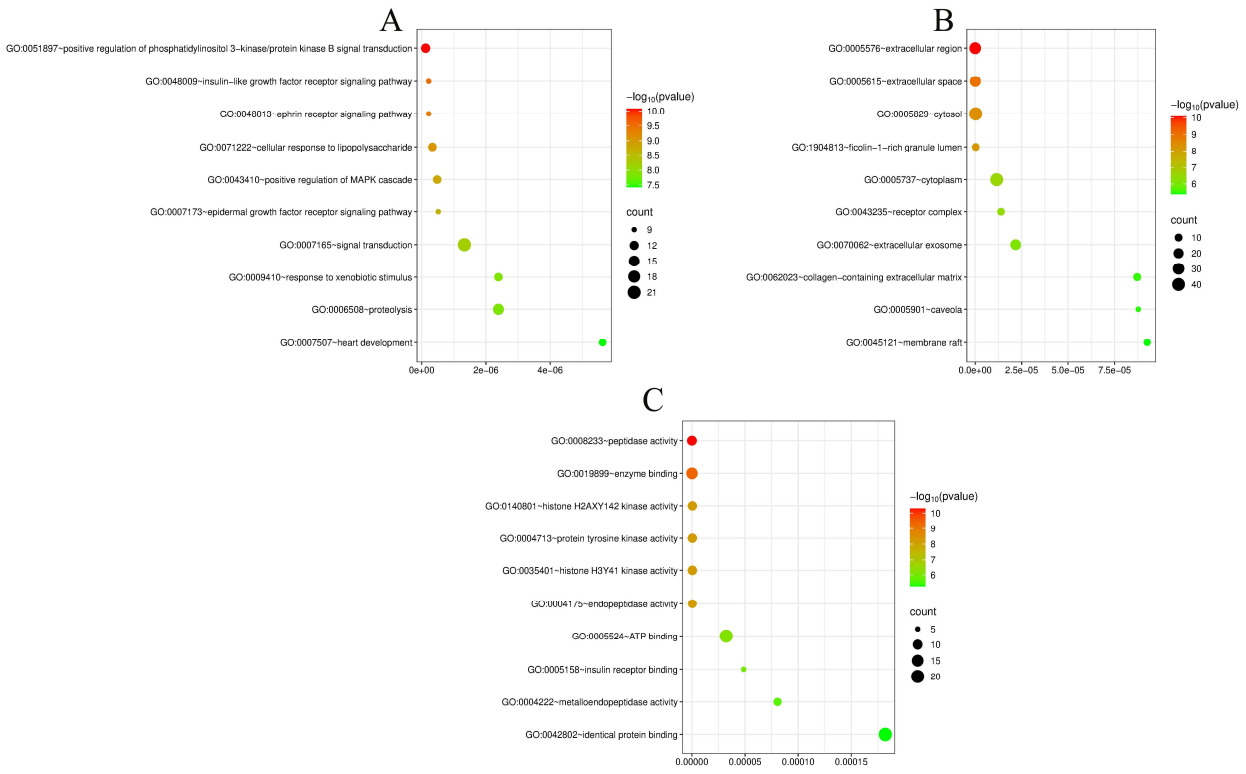

Fig. 5: GO pathway enrichment analysis of potential targets. (A) Biological process (BP); (B) Cellular component (CC); (C) Molecular function (MF).

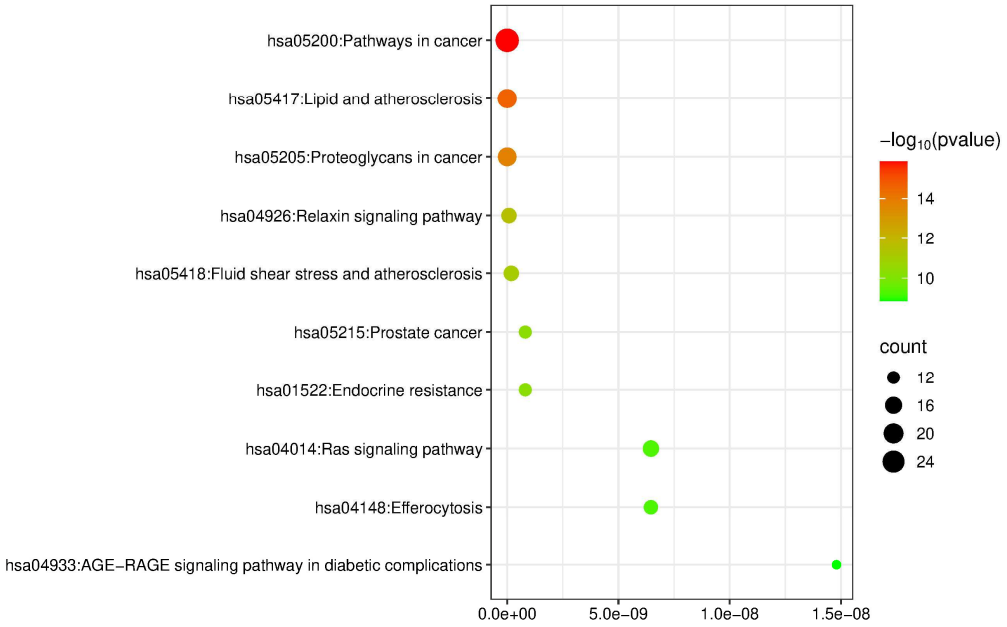

Fig. 6: KEGG enrichment analysis.

Table 1: Results of molecular docking between resveratrol and core targets (kcal/mol).

Target	Binding energy
EGFR	-8.4
SRC	-6.4
HSP90AA1	-6.8
ALB	-8.8

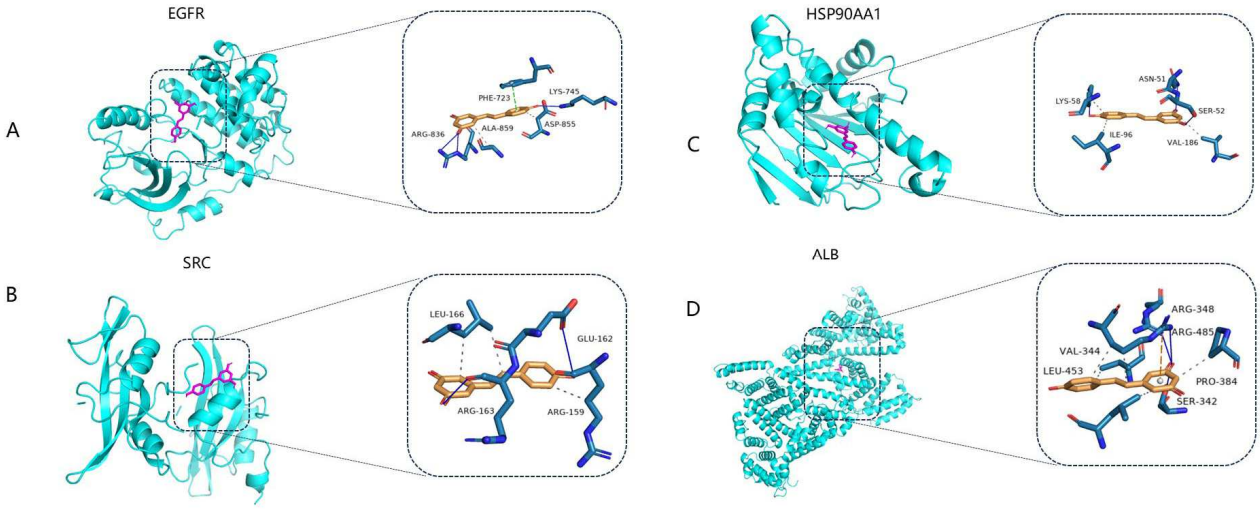

Fig. 7: Schematic diagram of molecular docking of resveratrol with core targets EGFR, SRC, HSP90AA1 and ALB. (A) EGFR; (B) SRC; (C) HSP90AA1; (D) ALB.

By leveraging network pharmacology and molecular docking technologies, the current study undertook a systematic investigation into the prospective targets and underlying mechanisms of resveratrol in combating RSV. A sum of 67 intersection targets of resveratrol and RSV were screened, including core targets such as EGFR, SRC, HSP90AA1 and ALB. Serving as an epidermal growth factor receptor, EGFR exerts a pivotal role in viral invasion and cellular signal transduction processes(Noh and Shin, 2023a). Previous studies have shown that EGFR activation may be involved in the replication process of RSV and the inhibitory effect of resveratrol on EGFR may block the key links of virus replication (Nadile *et al.*, 2022; Noh and Shin, 2023b). Activation of SRC represents a core step in viral invasion into host cells, directly promoting the progression of viral infection. Aberrant activation of SRC is closely associated with cellular pathological responses following viral infection (Lian *et al.*, 2025). The high-affinity binding between resveratrol and SRC suggests that it may reduce RSV-induced cell damage by inhibiting SRC activity (Liu *et al.*, 2024). As a host molecular chaperone, HSP90AA1 is involved in the correct folding and structural stability of RSV viral proteins. Proper folding of viral proteins is a prerequisite for RSV assembly, which directly affects the formation and release of viral particles (Lubkowska *et al.*, 2021). The binding of resveratrol to HSP90AA1 may interfere with the correct folding of viral proteins, thereby inhibiting viral assembly and release. ALB may exert indirect effects through immunomodulation, potentially regulating the host immune response to viral infection and enhancing antiviral immunity (Wiedermann, 2021). Therefore, ALB may not be a direct antiviral target. Its identification as a core target reflects the multi-target property of resveratrol and these targets may not be specific to respiratory syncytial virus (RSV), which is an inherent characteristic of network pharmacology-based multi-target analysis.

Functional enrichment analysis based on the GO database revealed that the intersecting targets are predominantly involved in key biological processes, including positive regulation of phosphatidylinositol 3-kinase/protein kinase B signal transduction and positive regulation of MAPK cascade. The phosphatidylinositol 3-kinase/protein kinase B signaling pathway is strongly correlated with cell survival and proliferation. RSV infection may promote its own replication by activating this pathway and the regulation of this pathway by resveratrol may inhibit viral proliferation (Liu *et al.*, 2026). The MAPK cascade reaction exerts a critical function in the inflammatory response caused by virus infection. The regulation of this pathway by resveratrol may reduce lung inflammation caused by RSV infection (Huang *et al.*, 2022; Jones *et al.*, 2025). Findings from KEGG pathway enrichment analysis indicated that the intersecting targets are predominantly enriched in cancer-related pathways, Ras signaling pathway, etc. Although some pathways are related to cancer, the role of the Ras signaling pathway in virus infection has

been confirmed (Sinha *et al.*, 2023). As an upstream regulator, the Ras pathway mediates early signal transduction during viral invasion, transmitting viral invasion signals into the cell (Liang *et al.*, 2025) and the inhibition of this pathway by resveratrol may be one of its important antiviral mechanisms. Viruses often hijack key host signaling pathways (including cancer-related ones) to complete their life cycle. These pathways are not cancer-specific. For example, the PI3K-Akt, MAPK and Ras pathways play critical roles in RSV infection by regulating key steps of the viral life cycle and host pathological responses. They are central to cell survival, inflammation and metabolism, all of which are essential for RSV pathogenesis (Liang *et al.*, 2025).

Molecular docking outcomes demonstrated that resveratrol exhibits favorable binding activity toward EGFR, SRC, HSP90AA1 and ALB, with binding energies all < -5 kcal/mol. These findings suggest that resveratrol may have strong potential binding interactions with these core targets, providing preliminary computational evidence supporting a possible molecular link underlying the anti-RSV effects of resveratrol.

Notably, this study differs from the recent work by, which focused on the direct binding of resveratrol to the RSV M protein (Rodrigues *et al.*, 2024). In contrast, the computational simulation analysis in this study complements these findings by revealing a host-mediated regulatory network, with EGFR, SRC, HSP90AA1 and ALB identified as the core host targets. These targets and their enriched pathways, including PI3K/Akt, MAPK and Ras, illustrate how resveratrol inhibits viral replication by modulating host cellular functions—an aspect not covered in previous experimental studies. Therefore, the findings of this study integrate viral target binding (from prior work) and host pathway regulation (from the present study), yielding a more complete mechanistic explanation for the anti-RSV activity of resveratrol.

Integrating existing experimental evidence and the predictive results of this study, resveratrol may exert anti-RSV effects through two pathways: Directly binding to the viral M protein to interfere with viral assembly (Rodrigues *et al.*, 2024) and targeting host proteins (EGFR, SRC, HSP90AA1, ALB) to regulate the PI3K-Akt, MAPK and Ras signaling pathways, thereby inhibiting viral replication and alleviating inflammatory responses. This dual mechanism strengthens the theoretical framework and provides a basis for subsequent combined target validation.

However, this study still has certain limitations. Firstly, as a purely computational simulation study, all targets, pathways and mechanisms identified are predictive results and need to be validated through *in-vitro*/*in-vivo* experiments. Secondly, molecular docking is an *in-vitro* simulation; the stable binding of resveratrol to core targets (such as EGFR, SRC, HSP90AA1) only provides a molecular basis for potential functional inhibition, while the direct causal relationship between resveratrol-target binding, target functional inhibition and subsequent RSV replication inhibition still needs to be further confirmed by cellular and animal experiments. Thirdly, the molecular docking analysis did not set positive controls, decoy molecules or additional validation steps (such as molecular dynamics simulation and binding mode verification); this defect is a limitation of preliminary computer simulation studies at this stage and future studies will supplement these key experimental design elements to validate the docking results. In addition, this study did not include clinical data, so it is too early to draw conclusions about the clinical application of resveratrol — any clinical translation must undergo strict preclinical and clinical validation.

In future studies, we will verify the regulatory effects of resveratrol on core targets and its inhibitory activity against RSV replication using *in-vitro* cell experiments (such as RSV-infected A549/HEp-2 cells). Target mRNA levels will be determined by qPCR and viral titers will be measured by plaque assay. *In-vivo* experiments will be performed using an RSV-infected mouse model to evaluate antiviral efficacy and pathway regulation. Furthermore, validation will be conducted by combining the viral M protein with host targets to explore synergistic antiviral effects.

In summary, this study employed network pharmacology and molecular docking to predict the core targets (EGFR, SRC, HSP90AA1, ALB) and related signaling pathways (PI3K-Akt, MAPK, Ras) underlying the inhibitory effects of resveratrol against RSV. However, the inferred potential mechanism of resveratrol against RSV represents a comprehensive deduction based on supportive evidence from molecular docking and existing literature on the biological functions of these targets.

Whether resveratrol can be practically applied for RSV treatment requires further validation of its antiviral efficacy and safety through *in-vitro* cell-based experiments and *in-vivo* animal models, followed by systematic preclinical pharmacodynamic and toxicological studies as well as clinical trials. At this stage, the present work only constitutes early theoretical exploration. Collectively, these findings provide a theoretical foundation for the preclinical validation of resveratrol and offer novel insights for the research and development of anti-RSV agents.

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None.

Authors' contributions
Jianbo Xia: Conceived and designed the research, methodology, formal analysis and drafted the original manuscript; Zuliang Shi: Contributed to data curation,

software application and visualization; Mengxin Shen: Drafted the original manuscript, data curation, software application, supervision, revised and reviewed the manuscript critically.

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Data availability statement
The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval
Not applicable.

Conflict of interest
The authors declare that they have no conflicts of interest.

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