Integrating network pharmacology and experimental validation to explore the potential mechanism by which resveratrol acts on osimertinib resistance in lung cancer

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Abstract. Globally, osimertinib resistance has been a long-term challenge. Resveratrol, a naturally occurring polyphenolic compound found in various plants, has the potential to modulate multidrug resistance mechanisms. However, the specific role of resveratrol in delaying osimertinib resistance in lung cancer is still unclear. The present study aimed to investigate the therapeutic effects and underlying mechanisms of resveratrol in delaying osimertinib resistance. Accordingly, the corresponding targets of resveratrol were screened through the Traditional Chinese Medicine Systems Pharmacology database. Similarly, the corresponding targets for osimertinib resistance were mined from the GeneCards database. A protein-protein interaction network was subsequently constructed to pinpoint key hub genes that resveratrol may target to delay resistance. Molecular docking analysis was then employed to assess the binding energy between the predicted key targets and resveratrol. Finally, *in vitro* experiments were performed to validate the results. Ultimately, 13 potential therapeutic targets of resveratrol related to delaying osimertinib resistance were identified. Kyoto Encyclopedia of Genes and Genomes analysis suggested that the effects of resveratrol may be associated with the apoptotic pathway. Molecular docking revealed that resveratrol has good binding affinities with MCL1 and BCL2L11. *In vitro* experiments confirmed that resveratrol inhibited the proliferation of osimertinib-resistant cells and upregulated the expression of BCL2L11. In conclusion, resveratrol may promote apoptosis by targeting BCL2L11 to delay osimertinib resistance.

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Introduction

Lung cancer is one of the most prevalent malignant diseases in the world, accounting for >10% of new cancer cases, and has the highest mortality rate among all cancer cases worldwide (1,2). Osimertinib, a third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), is widely used to treat EGFR-mutated non-small cell lung cancer (NSCLC) (3). Although osimertinib has high selectivity for EGFR-activating mutations and the EGFR T790M mutation in patients with advanced NSCLC, the development of drug resistance remains a major challenge (4). Drug resistance often indicates disease progression. Delaying resistance can slow tumor growth and reduce the risk of relapse and metastasis, allowing more patients to benefit from treatment and improve their quality of life (5). Therefore, novel therapeutic strategies for overcoming osimertinib resistance are urgently needed.

At present, various therapeutic approaches in combination with the administration of osimertinib, including the use of MET inhibitors, chemotherapy and immunotherapy, have been shown to be effective at prolonging the time to the development of resistance (6-8). Research has demonstrated that the overamplification of MET is a significant contributor to osimertinib resistance. The combination of MET inhibitors and osimertinib has been shown to be more effective for managing tumor progression (9). Chemotherapy remains a primary therapeutic approach for NSCLC. In patients with NSCLC that is resistant to EGFR inhibitors, timely chemotherapy interventions can serve as an effective treatment strategy. Evidence suggests that combining chemotherapy drugs, such as pemetrexed or cisplatin, with EGFR inhibitors can improve treatment effectiveness and prolong patient survival (10). In patients with resistant NSCLC, immune checkpoint inhibitors,

such as programmed cell death 1/programmed death-ligand 1 inhibitors, have been shown to have significant efficacy (11). This combined strategy can enhance the immune response to delay the onset of drug resistance (12).

Increasing evidence shows that the use of natural compounds can overcome osimertinib resistance in NSCLC (13,14). Resveratrol, a natural polyphenolic compound found in various plants, has gained considerable attention for its potential role in cancer prevention and treatment (15). Resveratrol is widely found in plants, including in blueberries, and the skins of grapes and peanuts (16), and has multiple beneficial characteristics, including antioxidant, anticancer, anti-inflammatory and immune-modulating properties (17). Moreover, a previous study has indicated that resveratrol has the potential to act as a regulator of multidrug resistance by inhibiting efflux transporters such as P-glycoprotein, multidrug resistance-associated proteins and breast cancer resistance proteins (18). Resveratrol can also enhance the antitumor ability of paclitaxel against NSCLC by regulating PTEN-induced kinase 1/Parkin-mediated mitophagy (19). (Z)3,4,5,4'-trans-tetramethoxystilbene, a novel derivative of resveratrol, selectively increases intracellular calcium levels to effectively suppress gefitinib-resistant NSCLC (20). Nevertheless, the molecular mechanism by which resveratrol delays osimertinib resistance remains to be elucidated. Therefore, it is necessary to elucidate the precise molecular targets of resveratrol to increase its specificity when targeting osimertinib resistance while minimizing off-target effects.

Network pharmacology, an emerging research field, integrates bioinformatics and pharmacology to examine the interplay between drugs and diseases (21). In previous years, it has been employed primarily for analyzing the potential mechanisms of action of natural products (22). Therefore, in the present study, network pharmacology combined with molecular docking was utilized to reveal the potential mechanisms by which resveratrol delays osimertinib resistance, and *in vitro* experiments were carried out to validate the results.

Materials and methods

Materials and reagents. Resveratrol (purity ≥98.0%) was purchased from NatureStandard (Shanghai Standard Technology Co., Ltd.; cat. no. ST00670120), prepared as a 100-mM stock solution with DMSO (Beyotime Institute of Biotechnology; cat. no. ST038) and diluted to different concentrations according to the experimental requirements. Osimertinib, purchased from Selleck Chemicals (cat. no. S7297), was reconstituted in DMSO. The solution was prepared to a concentration of 200 mM and stored at -20˚C to preserve its stability.

Collection of the targets of resveratrol and of osimertinib resistance in lung cancer. The potential targets of resveratrol were identified via searches of the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database (https://www.tcmspw.com/tcmsp.php) (23). The disease-related genes were obtained from the GeneCards (http://www.genecards.org) database (24), with the search term 'lung cancer osimertinib resistance'. The gene names were standardized via the UniProtKB database (https://www.uniprot.org/) (25). Subsequently, the targets associated with both resveratrol and osimertinib-resistant lung cancer were obtained.

Construction of the protein-protein interaction (PPI) network. The PPI network of the overlapping targets was established via the STRING database (https://string-db.org/) (26). With '*Homo sapiens*' as the chosen species and a confidence score of ≥0.4, the PPI network was visualized via Cytoscape (version 3.7.2) (27). The PPI network was subsequently analyzed and the hub targets with degrees above the median were filtered.

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses. To further determine the mechanism by which resveratrol delays osimertinib resistance in lung cancer, the biological functions and potential pathways involved were investigated. The Metascape database (www.metascape.org/) (28) was employed to perform GO and KEGG analyses on the hub targets identified from the PPI network. The results were visualized in the form of a bubble chart via the ggplot2 package (version 3.5.1) (29). The network of resveratrol, the common targets and the pathways were subsequently mapped via Cytoscape.

Molecular docking. The 3D model of resveratrol was retrieved from the PubChem database (30) and Chem3D software (version 20.1; library.bath.ac.uk/chemistry-software/chem3d) was utilized to minimize the energy of the structure. The protein structures of TP53 (4AGQ) (31), STAT3 (6NJS) (32), IGF1R (1P4O) (33), MCL1 (6OQC) (34) and BCL2L11 (1PQ1) (35) were subsequently extracted from the Protein Data Bank repository (www.rcsb.org) (36) and converted into the pdbqt format. Discovery Studio 2016 (Dassault Systèmes S.E.) was then employed for the processes of dehydration and hydrogenation, the modification of amino acid residues and energy minimization. The CDOCKER protocol within the software was applied to estimate the binding affinity between resveratrol and the target proteins. Finally, PyMOL (version 2.2.0; pymol.org/2/) was selected to visualize the molecular interactions.

Cell culture. PC9 cells, initially procured from The Cell Bank of Type Culture Collection of the Chinese Academy of Sciences, were cultivated in RPMI-1640 medium (HyClone; Cytiva; cat. no. SH30809.01) enriched with 10% fetal bovine serum (Gibco; Thermo Fisher Scientific, Inc.; cat. no. 10091148) and 1% penicillin-streptomycin (HyClone; Cytiva; cat. no. SV30010) at 37˚C in a humidified incubator with 5% CO_2 (Thermo Fisher Scientific, Inc.). Subsequently, osimertinib-resistant PC9 cells (PC9OR) were developed by gradually increasing the osimertinib concentration from 5 to 3,000 nM over a period of 5 months, as previously described (37). PC9OR cells were treated with osimertinib at a concentration of 3,000 nM to sustain the drug resistance.

Cell viability. The Cell Counting Kit-8 (CCK-8) assay (cat. no. C6005; NCM Biotech) was utilized to evaluate the viability of PC9OR cells after treatment with resveratrol. PC9OR cells were seeded in 96-well plates and exposed to different

concentrations of resveratrol (0, 10, 20, 40, 80 and 160 μM) for 48 h. A CCK-8 solution (10 μl/well) was subsequently added, and the cells were incubated for 2 h, after which the absorbance at 450 nm was measured with a spectrophotometer.

Colony formation assay. A total of 1,000 PC9OR cells were cultured in 6-well plates and then treated with 60 μM resveratrol for 2 weeks. Once visible colonies had formed (>50 cells per colony) (38), the plates were fixed with 4% paraformaldehyde (cat. no. BL539A; Biosharp Life Sciences) at room temperature for 30 min and stained with a 0.1% crystal violet solution (cat. no. C0121; Beyotime Institute of Biotechnology) for 15 min at room temperature. After staining, the plates were washed with PBS, dried and imaged, and then cells were counted using ImageJ (v1.8.0; National Institutes of Health).

Reverse transcription-quantitative PCR (RT-qPCR). PC9OR cells were plated in 6-well plates at a density of $5x10^3$ cells per well. After the cells had attached, 60 μM resveratrol was added for treatment for 48 h. Total RNA was extracted from PC9OR cells with the EZ-press RNA Purification Kit (EZBioscience; cat. no. B0004DP). cDNA was reverse transcribed using the PrimeScript™ RT reagent Kit (Takara Bio, Inc.; cat. no. RR037A). The reverse transcription conditions were as follows: 37˚C for 15 min, then 85˚C for 5 sec and finally cooling to 4˚C. For qPCR, PerfectStart® Green qPCR SuperMix (TransGen Biotech Co., Ltd.; cat. no. AQ601-02) was utilized. The qPCR thermal cycling parameters were set as follows: Preliminary denaturation at 95˚C for 30 sec, followed by 40 cycles of 95˚C for 15 sec and 60˚C for 60 sec. The quantification of mRNA levels was performed using the $2^{-\Delta\Delta Cq}$ method (39), and the results were further normalized against the expression levels of GAPDH. The specific sequences of the primers used were as follows: BCL2L11 forward, 5'-CTTGTG ACCCCAGCCAT-3' and reverse, 5'-CTTCCTTCCACTGCA CTAA-3'; Bcl-2 forward, 5'-GATTGTGGCCTTCTTTGAG-3' and reverse, 5'-GTTCCACAAAGGCATCC-3'; Bax forward, 5'-CCTGTGCACCAAGGTGCCGGAACT-3' and reverse, 5'-CCACCCTGGTCTTGGATCCAGCCC-3'; and GAPDH forward, 5'-GGAAGCTTGTCATCAATGGAAATC-3' and reverse, 5'-TGATGACCCTTTTGGCTCCC-3'. All primers were synthesized by Sangon Biotech Co., Ltd.

Western blotting (WB) analysis. PC9OR cells were treated with 60 μM resveratrol for 48 h and then lysed in ice-cold RIPA lysis buffer (Beyotime Institute of Biotechnology; cat. no. P0013B). The protein concentrations within the lysates were measured with a BCA Protein Assay Kit (Epizyme; Ipsen Pharma; cat. no. ZJ101). Proteins (20 μg/lane) were resolved through 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and then electrophoretically transferred onto polyvinylidene fluoride membranes. The membranes were blocked with a 5% milk solution at room temperature for 1 h, then incubated with primary antibodies (1:5,000) at 4˚C overnight. Afterwards, the membranes were incubated with a 1:5,000 dilution of HRP-conjugated goat anti-rabbit IgG secondary antibody (Proteintech Group, Inc.; cat. no. SA00001-2) for 1 h at 37˚C and visualized using an enhanced chemiluminescence solution (New Cell Molecular Biotech; cat. no. P10200). The analysis of the bands was conducted with ImageJ (v1.8.0; National Institutes of Health). The BCL2L11 antibody (cat. no. ET1608-14) was obtained from HUABIO, and the β-actin antibody (cat. no. 20536-1-AP) was purchased from Proteintech Group, Inc.

Statistical analysis. All data are displayed as the mean ± SD derived from a minimum of three separate experimental trials. GraphPad Prism 8.0 software (Dotmatics) was utilized for both plotting graphs and statistical analysis. All the results were calculated using the unpaired t-test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Collection of drug-disease overlapping targets. A flowchart illustrating the design of the present study is depicted in Fig. 1. A total of 151 target genes were initially obtained from the TCMSP database and 150 genes were retained from the UniProt database with standardized gene symbols. Specifically, the standardized gene symbols for the target genes PKA catalytic subunit C-α and protein kinase C α type were consistent, both being PRKCA. Simultaneously, 131 disease-related genes were identified from the GeneCards database. A total of 13 overlapping targets (TP53, BRCA2, IGF1R, STAT3, ABCG2, HGF, MCL1, CFLAR, BCL2L11, TNFRSF10A, TGFB2, SREBF1 and CDK7) were obtained when the resveratrol targets were compared with the disease-related targets. A PPI network was then built to identify the key targets (Fig. 2). The 5 targets with degree values >5 were screened as the key therapeutic targets, from 1 to 5 in the order of TP53, STAT3, IGF1R, MCL1 and BCL2L11.

Pathway enrichment analysis. To explore the potential mechanisms by which resveratrol delays osimertinib resistance, GO and KEGG analyses of the 13 genes derived from the PPI network were conducted (Fig. 3). The identified biological process terms included 'apoptotic signaling pathway' and 'cellular response to peptide'. The molecular function terms included 'protease binding', 'protein kinase binding' and 'kinase binding'. The cellular component terms included 'membrane raft' and 'membrane microdomain'. Moreover, the top 20 pathways were related to KEGG pathways including 'Pathways in cancer', 'Apoptosis' and 'EGFR tyrosine kinase inhibitor resistance' (Fig. 3B). Consequently, the apoptosis pathway was selected as a pivotal focus for subsequent investigation on the basis of this pathway enrichment.

Compound-target-pathway network construction. To visualize and elucidate the pharmacological potential of resveratrol for modulating osimertinib resistance, Cytoscape was utilized to construct a network of resveratrol-common target genes and KEGG pathways with 35 nodes and 93 edges (Fig. 4). Among the core target genes, TP53 (19 edges), STAT3 (13 edges), IGF1R (10 edges), MCL1 (4 edges), BCL2L11 (9 edges) and the apoptosis pathway (5 edges) had a high degree of connectivity, suggesting their involvement in the development of osimertinib resistance.

Molecular docking. Molecular docking simulations were performed with the 5 identified targets (TP53, STAT3,

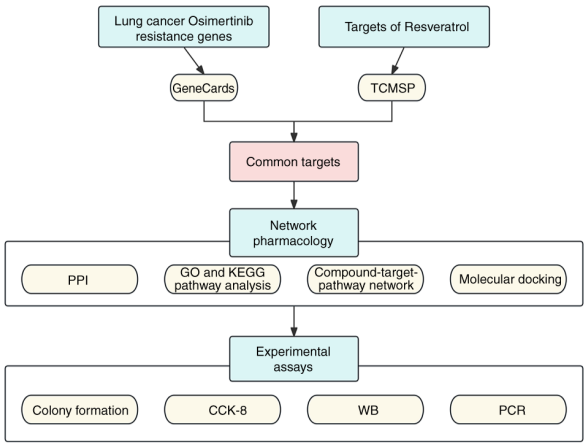

Figure 1. Flowchart of the study design. TCMSP, Traditional Chinese Medicine Systems Pharmacology; PPI, protein-protein interaction; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; CCK-8, Cell Counting Kit-8; WB, western blotting.

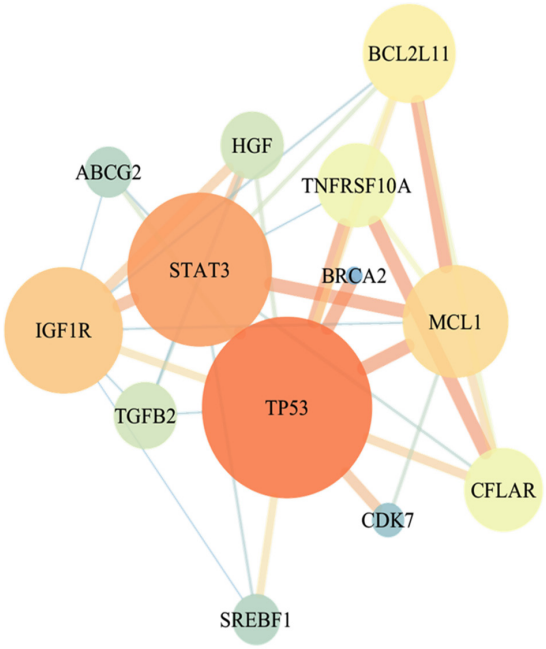

Figure 2. Protein-protein interaction network of overlapping targets between resveratrol and osimertinib resistance. The greater the degree, the larger the size, the deeper the color, and the more critical the target is considered to be.

IGF1R, MCL1 and BCL2L11) and resveratrol. It was found that resveratrol was predicted to bind to TP53, STAT3, IGF1R, MCL1 and BCL2L11 with energies of -5.9, -6.0, -6.5, -7.9 and -7.3 kJ/mol, respectively (Fig. 5). The smaller the binding energy is, the better the binding activity between the ligand and receptor. When the binding energy is <-7 kcal/mol, this signifies a strong binding affinity (40). Therefore, resveratrol may have strong binding affinities with MCL1 and BCL2L11, indicating that the mechanism by which resveratrol delays osimertinib resistance may be closely linked to binding to these targets. Furthermore, the distribution of the targets of resveratrol in the apoptosis pathway was mapped, and it was found that resveratrol can regulate the apoptosis pathway by targeting MCL1 and BCL2L11 (Fig. 6).

Resveratrol inhibits the proliferation of osimertinib-resistant lung cancer cells. To verify the results of the network pharmacological analysis, *in vitro* experiments were conducted. Various concentrations of resveratrol (0-160 μM) were used to treat PC9OR cells for 48 h and cell viability was determined via a CCK-8 assay. The results showed that resveratrol significantly reduced the cell viability of PC9OR cells, with an IC_{50} of ~60 μM (Fig. 7A). Furthermore, resveratrol inhibited the long-term proliferation of PC9OR cells (Fig. 7B) and led to a notable alteration in the morphology of PC9OR cells, resulting in a flattened appearance (Fig. 7C).

Resveratrol upregulates the expression of BCL2L11. RT-qPCR was performed to confirm whether resveratrol delays osimertinib resistance through the targets identified via network pharmacology (MCL1 and BCL2L11). Resveratrol increased the mRNA expression levels of BCL2L11 in PC9OR cells ($P<0.001$) (Fig. 7D). Notably, resveratrol decreased the expression levels of MCL1, but there was no significant difference ($P>0.05$). Concurrently, resveratrol reduced the mRNA expression levels of Bcl-2 and increased the expression levels of Bax ($P<0.001$) (Fig. S1). Furthermore, resveratrol increased the protein expression levels of BCL2L11 in PC9OR cells (Fig. 7E). These findings demonstrated that resveratrol might promote apoptosis to delay osimertinib resistance.

Discussion

Globally, osimertinib resistance has been a long-term challenge. Despite the implementation of drug combination therapy, immunotherapy and individualized treatment approaches in clinical practice, significant breakthroughs in addressing drug resistance have not been achieved (41). Thus, exploring novel strategies to overcome osimertinib resistance is crucial. To overcome this difficulty, complementary and alternative therapies, including the use of herbal compounds, natural compounds or medicinal plant monomers to delay drug resistance, have become the focus of research. Resveratrol inhibits tumor cell proliferation and viability through diverse mechanisms (42). Resveratrol has also been reported to demonstrate anti-oxidizing and anti-inflammatory properties (43,44). Moreover, resveratrol can modulate multiple signaling pathways involved in cell cycle regulation, apoptosis and other key cellular processes to impact the biological behavior of tumor cells (45). Furthermore, resveratrol has been shown to enhance the sensitivity of cells to chemotherapy drugs, and resveratrol-based nanoparticles can reverse multidrug resistance (46-48). However, the effects of resveratrol on osimertinib resistance in lung cancer and the underlying mechanisms have not been evaluated. In the present study, it was observed that resveratrol inhibited the viability of osimertinib-resistant lung cancer cells, potentially by inducing apoptosis.

Apoptosis, a subtle and energy-dependent form of cell death, represents the primary mechanism by which most cells in the body naturally perish, and does not cause an inflammatory response (49). Apoptosis plays a crucial role in the

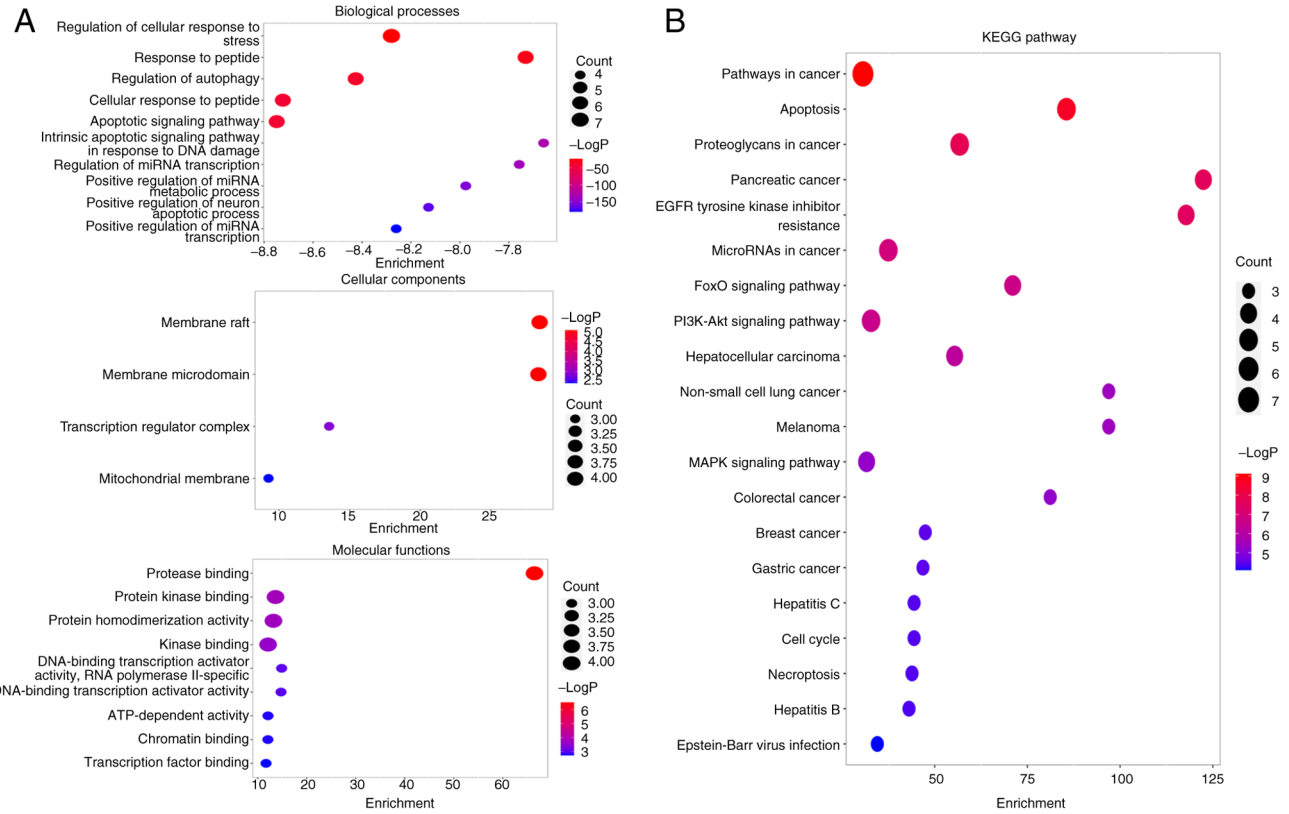

Figure 3. GO and KEGG analyses. (A) The GO terms of resveratrol against osimertinib resistance. (B) The top 20 pathways affected by resveratrol against osimertinib resistance. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

development and occurrence of lung cancer (50). However, during the progression of lung cancer, tumor cells frequently evade apoptosis, leading to tumor growth and metastasis (51). Moreover, abnormal apoptosis is closely associated with drug resistance in cancer therapies (52,53). Various therapeutic approaches, including chemotherapy, targeted therapy and immunotherapy, aim to inhibit tumor growth by promoting apoptosis. Nevertheless, lung cancer cells employ diverse mechanisms to evade apoptosis, resulting in the development of drug resistance (54). These mechanisms include the regulation of apoptosis-related protein expression, the modulation of apoptosis signaling pathways and the upregulation of cell survival signals (55). In the present study, network pharmacology and molecular docking were employed to predict the involvement of resveratrol in regulating osimertinib resistance by promoting apoptosis. Furthermore, PC9OR cells were utilized as an *in vitro* model of osimertinib resistance in lung cancer. The present study demonstrated that resveratrol significantly suppressed the proliferation of PC9OR cells, upregulated the expression of BCL2L11 and promoted cellular apoptosis.

BCL2L11 has potent proapoptotic properties and is categorized within the BCL2 protein family (56). BCL2L11 plays a crucial role in maintaining the balance of apoptosis in T-cell and B-cell homeostasis (57). Impairment of the EGFR-TKI-mediated apoptosis pathway (BCL2L11 deletion polymorphism) can lead to resistance to EGFR-TKIs (58). Research has revealed that sensitivity to gefitinib can be restored by upregulating the expression of BCL2L11 (59). Therefore, these studies suggest that upregulating BCL2L11

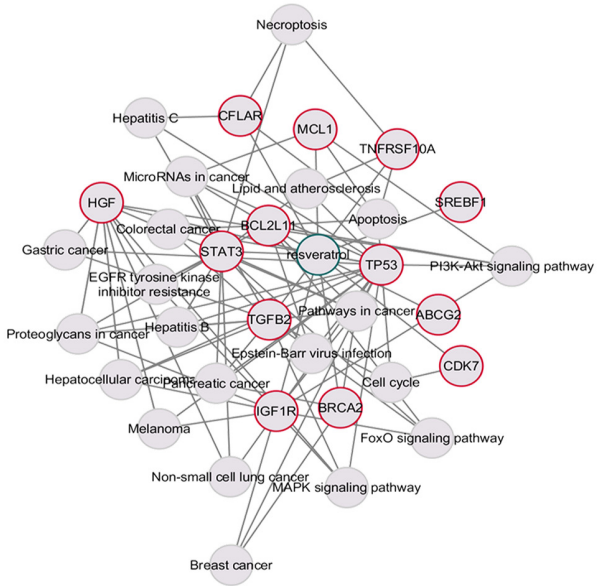

Figure 4. Compound-target-pathway network of resveratrol constructed by Cytoscape. Red circles represent 13 overlapping targets, the green circle represents resveratrol and gray circles represent 20 pathways.

delays the development of drug resistance. Additionally, these findings indicate that, through the examination of gene expression patterns in patients, it may be possible to identify patients with NSCLC who are likely to benefit from resveratrol treatment, enabling individualized treatment. Concurrently, these data can inform the future direction

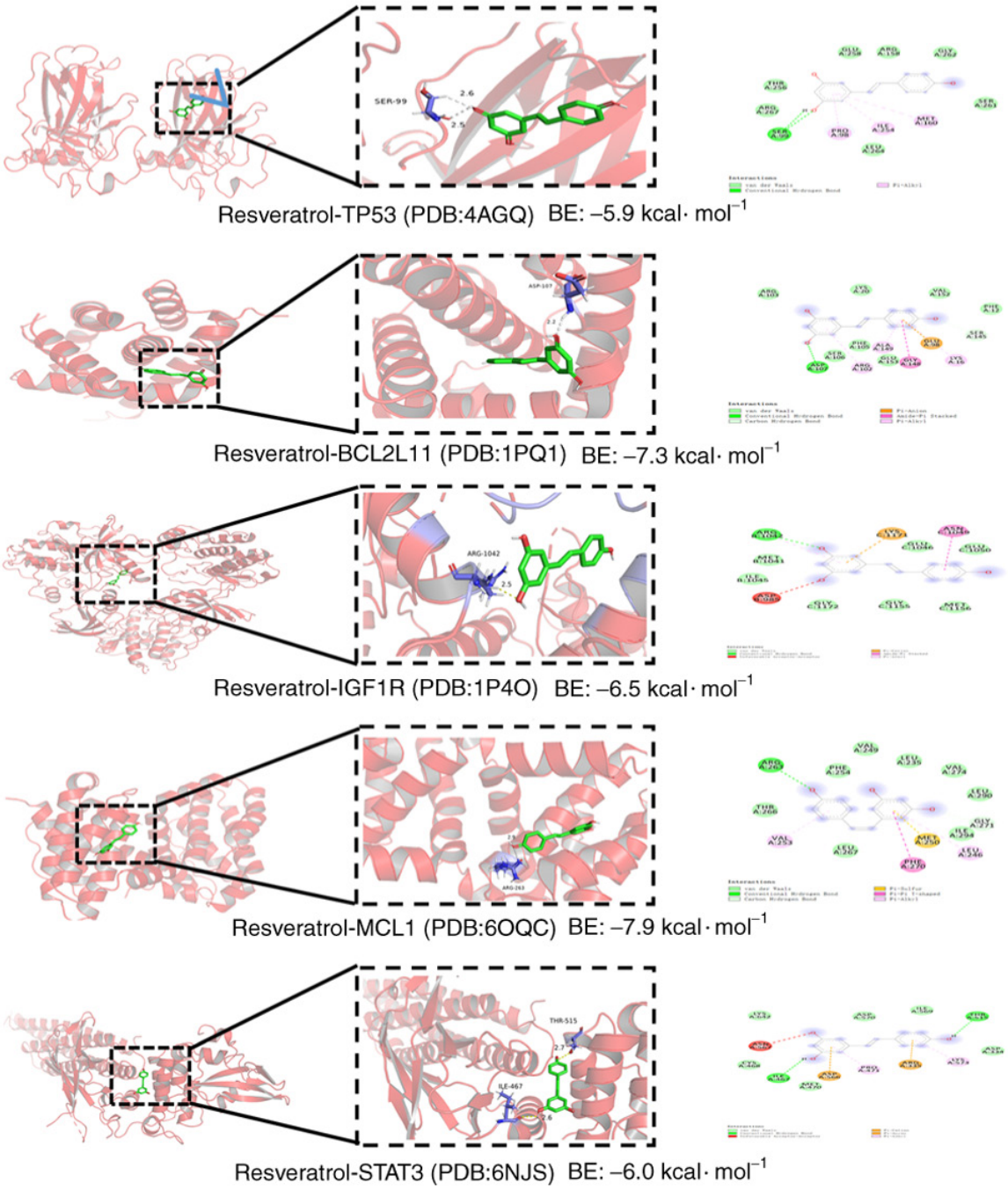

Figure 5. Docking models of resveratrol with TP53, STAT3, IGF1R, MCL1 and BCL2L11. BE, binding energy.

of drug and molecular inhibitor development aimed at combating resistance in lung cancer. Moreover, the present study established resveratrol as a candidate for reversing drug resistance, laying the groundwork for the design of clinical trials. Resveratrol has the potential to prolong the duration of the response to osimertinib, defer the emergence of resistance and ultimately enhance the therapeutic outcomes for patients.

To summarize, the present study employed network pharmacology and molecular docking to investigate the potential of resveratrol to delay the development of osimertinib resistance by modulating apoptosis. Following *in vitro* experiments, it was confirmed that resveratrol increased the expression of BCL2L11 in PC9OR cells, confirming its ability to delay osimertinib resistance by inducing cell apoptosis.

This study has several notable advantages. First, a network pharmacological analysis that leveraged various databases, including TCMSP and GeneCards, was conducted. This cross-database integration enhanced the thoroughness and precision of the screening methodology, which was crucial for identifying a broader range of potential targets. Moreover, the identified targets were substantiated via molecular docking and *in vitro* assays. This synergistic approach of computational analysis and experimental validation bolsters the credibility of the results and confirms that resveratrol was an inhibitor of osimertinib resistance. To the best of our knowledge, the

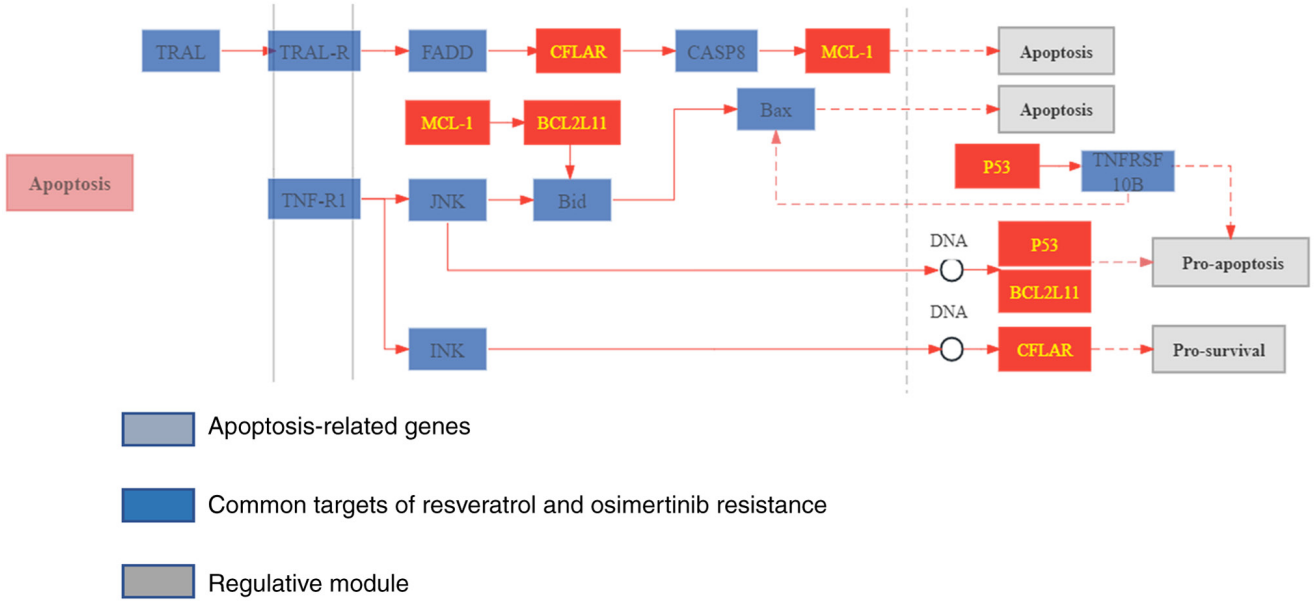

Figure 6. Network of interactions involving resveratrol targets within the apoptosis pathway. Red rectangles represent 4 genes related to the apoptosis pathway.

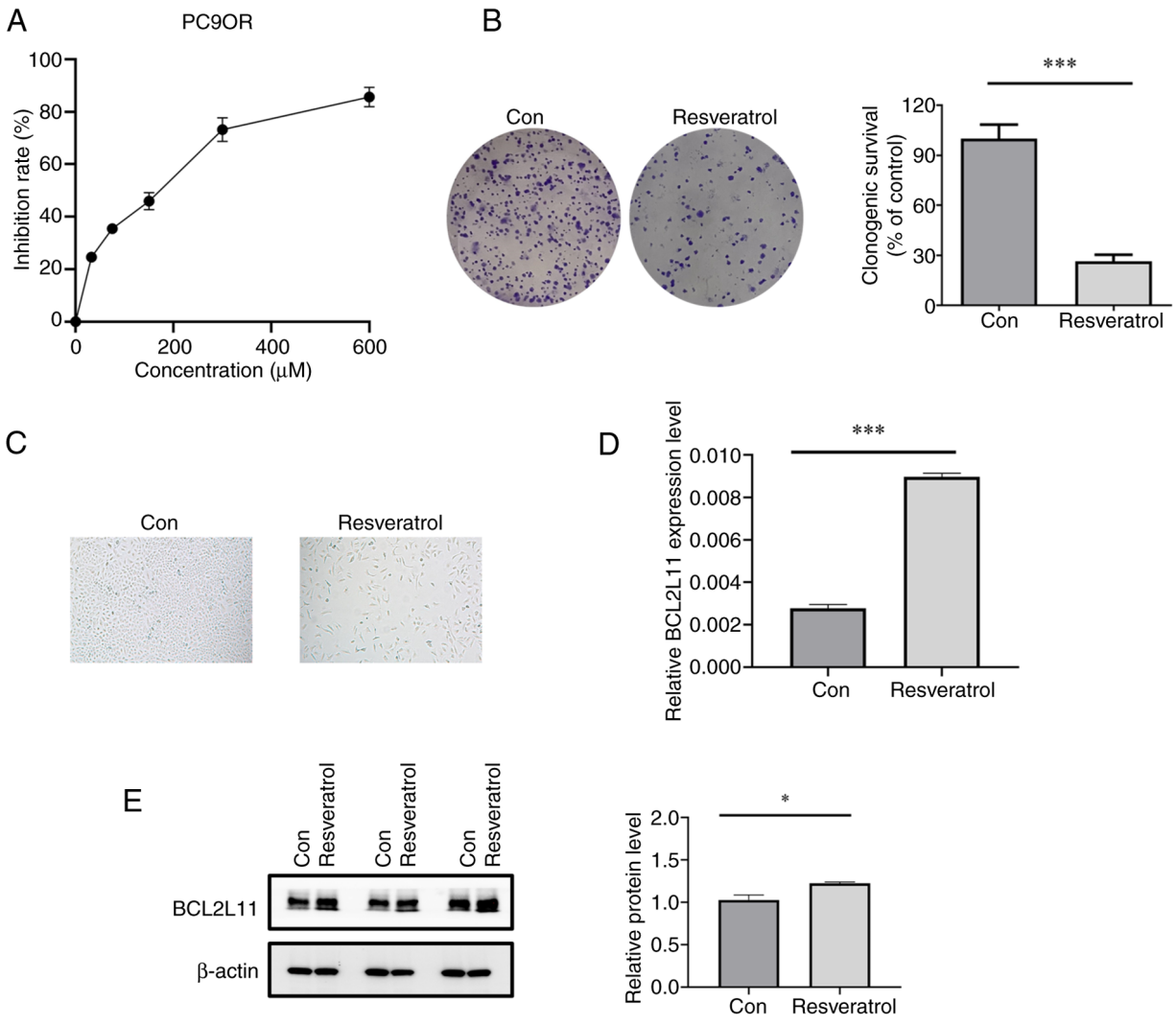

Figure 7. Effect of resveratrol on PC9OR cells. (A) Cell Counting Kit-8 and (B) colony formation assays were used to detect the effect of resveratrol on the proliferation of PC9OR cells. (C) Morphology of PC9OR cells in each group after 48 h (magnification, x20). Effect of resveratrol on BCL2L11 (D) mRNA and (E) protein expression levels in PC9OR cells. The experiments were repeated at least three times. The unpaired t-test was applied for statistical significance, *P<0.05, ***P<0.001. Con, control; PC9OR, osimertinib-resistant PC9 cells.

current study represents a groundbreaking effort in the comprehensive identification and validation of the administration of resveratrol as a therapeutic approach to overcome osimertinib resistance. The present study addresses a gap in the literature and offers researchers a basis for further exploration.

However, the present study has certain limitations. First, molecular docking serves merely as a predictive measure with regard to the binding stability between small and large molecules. Additionally, the bioavailability of resveratrol is influenced by a multitude of factors, including drug metabolism, distribution and excretion, which requires further exploration. Second, although the tumor-inhibiting effect of resveratrol has been revealed, the safe dosage remains uncertain. For this reason, the potential toxicity of this drug needs to be carefully assessed. Furthermore, there is limited clinical evidence supporting the efficacy of resveratrol for combating resistance to osimertinib. Finally, the present study did not include a comparison between resveratrol and osimertinib or their combination. This will be a promising direction for future research. Additionally, more in-depth studies will further clarify the specific mechanisms by which resveratrol delays osimertinib resistance, which is eagerly anticipated.

In conclusion, the present study revealed that resveratrol could delay osimertinib resistance by targeting BCL2L11, which was identified as a key target, and by inducing apoptosis. The present study revealed the potential therapeutic value of resveratrol for the treatment of osimertinib-resistant lung cancer, laying a foundation for the clinical application of resveratrol.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XY, SLS and HLZ designed the study. XY, YY and HWZ performed the experimental work. JTZ and NNZ conducted the data analyses. SLS and HLZ revised the manuscript and confirmed the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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