

## Investigating the mechanism of action of grape active compounds in treating non-small cell lung cancer (NSCLC) through a network pharmacology and molecular docking approach

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### ABSTRACT

Although *Vitis vinifera* is a major fruit crop with well-established nutritional and therapeutic qualities, little is known about its possible anti-cancer benefits. This study examined the mechanisms of action in the treatment of non-small cell lung cancer (NSCLC) using a network pharmacology and molecular docking method. A total of 456 potential protein targets were obtained from the identification of ten major bioactive chemicals, including ascorbic acid, citric acid, succinic acid, caffeic acid, and chlorogenic acid. 149 genes overlapped when 5,941 NSCLC-related targets from GeneCards were integrated. The protein-protein interaction (PPI) network analysis identified ten key hub proteins (e.g., *EGFR*, *ESR1*, *CASP3*), with interaction scores ranging from 73 to 53. Molecular docking revealed strong binding affinities between key compounds and hub proteins, most notably citric acid and *EGFR* (-10.75 kcal/mol) and chlorogenic acid and *ESR1* (-6.85 kcal/mol). Stability was further supported by the presence of 2 to 7 hydrogen bonds in each complex. Survival analysis indicated that *PTGS2* overexpression significantly correlates with poor prognosis ( $p = 0.029$ ). Significant participation in cell proliferation, apoptosis control, inflammatory pathways, and cancer-related signalling cascades was shown by Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment studies. Strong binding affinities between important chemicals and hub proteins were shown by molecular docking, indicating that these compounds may have a pharmacological effect. *GEPIA*-based survival study revealed an overexpression of major oncotargets and the association between *PTGS2* expression and overall survival of patients with NSCLC. These results establish a basis for additional experimental validation and medication development while offering molecular insights into *V. vinifera*'s anti-NSCLC potential.

**Keywords:** Grape, Anticancer; Protein-protein interaction, Caffeic acid, Chlorogenic acid

## Introduction

About 2.2 million new instances of lung cancer (LC) are reported each year, and LC accounts for roughly 18% of all cancer-related deaths worldwide, making it one of the most common and fatal cancers (Schabath & Cote, 2019; Sung et al., 2021). Non-small cell lung cancer (NSCLC) is the most common subtype of LC, accounting for approximately 85% of cases, while small cell lung cancer makes up the remaining 15% (Liu et al., 2022; Zhou, 2019). Despite advancements in surgery, chemotherapy, radiation, targeted therapy, and immunotherapy, the five-year overall survival rate for LC remains below 20%, largely due to late-stage diagnosis and limited therapeutic effectiveness (Dasari et al., 2022; Lei et al., 2023). In some regions, the five-year survival rate for NSCLC can be as low as 5%, highlighting the urgent need for more effective treatment strategies (Tang et al., 2025; Zhu et al., 2020).

Current treatment regimens often face challenges due to adverse effects, medication resistance, and the limited effectiveness of single-target therapies (Su et al., 2020). Long-term efficacy is jeopardised since the majority of targeted treatments only impact one route. Finding and creating new therapeutic compounds with clear mechanisms, little toxicity, and multi-target effectiveness is therefore crucial (Dasari et al., 2022; Shang et al., 2023; Zhang et al., 2023). Natural chemicals have recently gained increased interest as potential substitutes or supplements to traditional cancer treatments due to their ability to target multiple mechanisms, lower toxicity, and favourable safety profiles. In NSCLC models, traditional medicinal formulations like aloin, osthole, and sijunzi decoction have demonstrated promising anticancer properties (Gao et al., 2022; Jiang et al., 2023; Shang et al., 2023).

*Vitis vinifera* (grape), a fruit high in bioactive phytoconstituents such as flavonoids, phenolic acids, proanthocyanidins, and stilbenes such as resveratrol, is one such natural contender (Güler, 2023). These abundant substances have shown anti-cancer benefits through a variety of methods, such as the reduction of pro-inflammatory mediators, the activation of apoptosis, the inhibition of mitosis, and the enhancement of antioxidant activity (Antonacci D, 2014; Forni et al., 2019; Usman et al., 2022). The anti-tumour benefits of *V. vinifera* and its extracts have been confirmed in several investigations, including hepatocellular carcinoma, oral squamous carcinoma, skin cancer, prostate cancer, and breast cancer. In MCF-7 breast cancer cells, for instance, grape seed extract (GSE) caused apoptosis (Hakimuddin et al., 2006), and resveratrol has been demonstrated to alter a number of signalling pathways implicated in the development of cancer (Sinha et al., 2016). By

downregulating the fatty acid-binding protein 5 gene, proanthocyanidins in prostate cancer were reported to reduce cell proliferation and increase apoptotic activity (Sei-ichi et al., 2019). *V. vinifera* extracts also reduced the growth of A431 cells in skin cancer models through cytotoxic actions and enhanced reactive oxygen species (ROS) generation (Decean et al., 2016; Grace Nirmala et al., 2018). Furthermore, by activating caspase-3 and causing ROS-mediated apoptosis, grape cane extract decreased the viability of hepatocellular carcinoma (HepG2 and Hep3B) cells (Aja et al., 2020). In oral squamous carcinoma, GSE induced DNA fragmentation and apoptotic cell death with an IC<sub>50</sub> of 245.98 µg/ml (Aghbali et al., 2013).

Ascorbic acid has been implicated in the modification of tumour microenvironments and redox states (Maekawa et al., 2022), which could be beneficial against NSCLC by mitigating the adverse effects of ROS and potentially reversing chemoresistance. Similarly, the role of citric acid in regulating metabolic pathways is crucial, as dysregulation of the citric acid cycle—particularly through metabolites like isocitrate and succinate—contributes to drug resistance in cancer (Wang et al., 2022). Succinic acid, acting as an oncometabolite, has been shown to inhibit prolyl hydroxylase and stabilise hypoxia-inducible factors (HIFs), thereby encouraging tumour growth and perpetuating a hypoxic environment conducive to cancer cells' survival (Baryła et al., 2022). Furthermore, the antioxidant properties of phenolic compounds like caffeic acid and chlorogenic acid are supported by literature for their ability to modulate inflammatory pathways, reduce cancer cell proliferation, and enhance apoptotic pathways (Murai & Matsuda, 2023). However, neither in vitro nor in silico studies have investigated the effects of *V. vinifera* constituents against NSCLC.

A potent method for investigating the intricate pharmacological effects of *V. vinifera* is network pharmacology. Drug-disease interactions spanning numerous targets may be investigated by combining systems biology, bioinformatics, and computational approaches. Network pharmacology assesses the interaction of several targets and pathways, in contrast to the conventional "one-drug-one-target" approach (Hopkins, 2008). It also makes use of machine learning and interaction networks that connect illnesses, genes, targets, and medications in order to comprehend system-level behaviours and pinpoint important therapeutic nodes (Zhang et al., 2024; Zhou et al., 2020). Molecular docking forecasts ligand-target interactions by modelling atomic-level interactions between chemi-

cals and proteins, identifying the ideal conformations of ligand-receptor complexes, and calculating their binding affinities (Zemnou, 2025).

While previous studies have extensively documented the general antioxidant and anti-inflammatory properties of *V. vinifera*, its systemic mechanism of action against NSCLC remains insufficiently explored through multi-target approaches. Existing literature often focuses on single compounds or broad cancer categories; however, our study distinguishes itself by employing an integrated network pharmacology and molecular docking framework to pinpoint the synergistic effects of specific bioactive compounds from *V. vinifera*. The goal of this study was to provide scientific insights into how this natural substance may regulate several pathways connected to the growth of NSCLC, further identifying potential therapeutic targets for future research.

## Materials and Methods

### *Identification of Active Ingredients and Target Genes in V. vinifera Grapes*

Primary bioactive components of *V. vinifera* were characterised previously through HPLC (Güler, 2023) and their chemical structures were obtained from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>). The SwissTargetPrediction program (<http://www.swisstargetprediction.ch/>) was used to anticipate their possible targets, and Microsoft Excel was used to consolidate and arrange all pertinent information. Then, using Cytoscape 3.10.2 (<https://cytoscape.org/>), a compound-target interaction network was built using the anti-NSCLC targets of *V. vinifera*'s main compounds. This allowed for the display and ranking of compounds according to the number of anticipated targets.

### *Screening for NSCLC and Drug-Disease Intersection Targets*

The GeneCards database (<https://www.genecards.org/>) was used to identify NSCLC-related targets. For additional analysis, the NSCLC-related gene set and the *V. vinifera* targets set were imported into a Venn Diagram (<https://bioinformatics.psb.ugent.be/webtools/Venn/>). The intersecting gene targets were used to determine the primary treatment targets.

### *Analysis of Protein-Protein Interactions (PPI) and Screening for Core Targets*

A PPI network was created in order to find interacting proteins. With the organism set to "Homo sapiens" and a minimum interaction score threshold of 0.4, the STRING database

(<http://string-db.org>) was used to build the PPI network associated with *V. vinifera*'s anticancer effects. The "Send Network to Cytoscape" option of the STRING program was then used to export the network straight to Cytoscape. Cytoscape plugins CytoHubba and MCODE were used to examine important topological metrics and find possible treatment targets.

### *Pathway Enrichment Analysis Using Kyoto Encyclopaedia of Genes and Genomes (KEGG) and Gene Ontology (GO)*

DAVID Database (<https://davidbioinformatics.nih.gov/>) was used to functionally analyse the shared targets of *V. vinifera* and NSCLC, and SRplot to design the graph. The three main modules of the GO enrichment research are the cellular component (CC), molecular function (MF), and biological process (BP). A KEGG pathway analysis was conducted in order to have a deeper understanding of the interactions and activities of these targets.

### *Molecular Docking of Active Compounds With Specific Targets*

The crystal structures of the five key target proteins were retrieved from the Protein Data Bank (<https://www.rcsb.org/>) and prepared using AutoDock 4.0 (Morris et al., 2009). Prior to storing the structures in pdbqt format, polar hydrogens were inserted, missing atoms were examined and fixed, and Gasteiger and Kollman charges were allocated. The nine active chemicals, meanwhile, were obtained in SDF format from the PubChem database, optimised for energy reduction using Chem3D v14.0, and then translated to PDB format using Open Babel (<https://sourceforge.net/projects/openbabel/files/openbabel/2.4.0/>). After that, the optimised ligands were loaded into AutoDock 4.0, where they were stored in pdbqt format, and their roots and torsions were determined. A grid box surrounded each target protein's active site to facilitate docking simulations. A population size of 300, 27,000 generations, 1,000,000 evaluations, and 100 GA runs were used to determine the Genetic Algorithm (GA) parameters (Zemnou et al., 2025). After each target was docked against the chosen compounds, post-docking analysis was used to determine the optimal binding postures. Discovery Studio Client v21.1 was used to display better and evaluate protein-ligand interactions.

### *Analysis of Core Target Gene Expression and Survival*

The expression patterns of the top ten core anti-NSCLC target genes in NSCLC were examined using the Gene Expression Profiling Interactive Analysis (GEPIA) database (<http://gepia.cancer-pku.cn/>). The assessment of the correlation between these genes' expression levels and patient outcomes,

more especially, overall survival (OS) and disease-free survival (DFS), was made easier by GEPIA. Hazard ratios (HRs) and 95% CIs were obtained from the Cox proportional hazards model, and survival analyses were performed using the Log-rank test. Patients were divided into groups with high and low expression levels based on the median expression value of 50%. Statistical significance was defined as a p-value of less than 0.05.

## Results and Discussion

### Active Ingredients and Target Genes for *V. vinifera*

The 10 most abundant chemicals from almost every genotype of *V. vinifera* were chosen for this investigation (Table 1). An Excel datasheet with the anticipated targets for every compound obtained from SwissTargetPrediction was created, and duplicate entries were eliminated. A total of 456 possible *V. vinifera* targets were obtained using this procedure. The links between the chosen compounds and their related targets are highlighted in Figure 1, which shows the active ingredient–drug target network created with Cytoscape 3.10.2.

**Table 1.** The top key active ingredients ranked by the degree method

| Numero | Names            | PubChem ID | Target Score |
|--------|------------------|------------|--------------|
| 1      | Caffeic acid     | 689043     | 100          |
| 2      | Chlorogenic acid | 1794427    | 100          |
| 3      | Citric acid      | 311        | 64           |
| 4      | Succinic acid    | 1110       | 62           |
| 5      | Ascorbic Acid    | 54670067   | 45           |
| 6      | Malic acid       | 525        | 36           |
| 7      | Tartaric Acid    | 444305     | 35           |
| 8      | Fumaric acid     | 444972     | 7            |
| 9      | Gallic acid      | 370        | 7            |
| 10     | Catechin         | 9064       | 0            |

### NSCLC Targets and Drug-Disease Intersection Targets

There were 5,941 predicted targets linked to NSCLC found in the GeneCards database. The compound target list has 253 distinct targets left after duplicate items were eliminated. 149 overlapping targets were identified using a Venn diagram analysis that combined the active chemical targets with the NSCLC target list; these targets were thought to be possible therapeutic gene targets (Figure 2).

### Analysing Protein Interactions and Searching for Important Targets

A PPI network with 1,391 edges and 149 nodes was created by entering the 149 possible targets into the STRING 12.0 database (<http://string-db.org>) (Figure 3A and 3B). The important interactions were then shown by importing the network into Cytoscape 3.10.2. The colours of the nodes varied from yellow (high degree value) to red (low degree value). The top 10 hub proteins were determined by degree centrality and are *EGFR*, *ESR1*, *CASP3*, *PPARG*, *JUN*, *SRC*, *STAT3*, *EP300*, *PTGS2*, and *MMP9* (Table 2; Figure 3C). These proteins serve as the primary therapeutic targets for the treatment of NSCLC using bioactive chemicals from grapes.

### GO and KEGG Pathway Enrichment Results Analysis

GO and KEGG pathway enrichment analysis of the top 10 intersecting targets, using an adjusted filter with a P-value < 0.05, further investigated the anti-NSCLC advantages of *V. vinifera*'s active ingredients and associated molecular processes. BP, MF, and CC were shown to be the 10 most enriched GO elements. The findings are displayed in Figure 4. RNA polymerase II's negative regulation of transcription, RNA polymerase II's positive regulation of transcription, the positive regulation of the apoptotic process, signal transduction, and other biological processes (BP) are affected by the main active substances' anti-NSCLC targets. Moreover, several cellular components (CC), including the cytoplasm, cytosol, nucleus, nucleoplasm, and others, are associated with the targets used in the treatment of NSCLC with the medications of *V. vinifera*. Furthermore, a range of molecular functions (MF), such as enzyme binding, identical protein binding, DNA binding, chromatin binding, and others, are implicated in the targets that *V. vinifera*'s chemicals use to affect NSCLC.

A dot map representing the top 10 KEGG pathways is also shown in Figure 4. These bioactive compounds may have anti-NSCLC properties through main molecular mechanisms such as pathways in cancer, hepatitis B, lipid and arteriosclerosis and proteoglycans in cancer. The most pertinent pathways have been described in Figure 5 below.

### Molecular Docking Analysis

Three important target proteins, *EGFR* (PDB ID: 7U98), *CASP3* (PDB ID: 1RHJ), and *ESR1* (PDB ID: 2BJ4) and

five important bioactive chemicals from *V. vinifera* were shown to interact significantly, according to molecular docking research. Protein–ligand interaction diagrams are shown in Figure 6, and Table 3 summarises the docking data. ESR1 showed strong binding affinities for ascorbic acid (−5.69 kcal/mol), caffeic acid (−6.05 kcal/mol), and chlorogenic acid (−6.85 kcal/mol). All five chemicals showed significant affinity for EGFR, although citric acid had the greatest interaction (−10.75 kcal/mol). On the other hand, CASP3 only exhibited significant affinity with chlorogenic acid (−5.91 kcal/mol) and caffeic acid (−5.68 kcal/mol).

In the top ten protein–ligand complexes, hydrogen bonds were the most common kind of interaction (Figure 6). At least two to seven hydrogen bonds, which are known to be essential for molecular recognition and significantly enhance the stability of protein–ligand complexes, were present in all 10 complexes. The binding stability and specificity were further improved by the presence of other non-covalent interactions in addition to hydrogen bonds, including van der Waals, Pi–sigma, Pi–sulfur, Pi–cation, and Pi–alkyl/alkyl interactions.

### Expression of Anti-NSCLC Core Targets

The expression levels of the top ten anti-HCC core targets, EGFR, ESR1, CASP3, PPARG, JUN, SRC, STAT3, EP300, PTGS2, and MMP9, were examined in both normal tissue samples and NSCLC of LUAD (lung adenocarcinoma) using the GEPIA2 database (Figure 7A). The observed variations in these key targets' expression between normal and NSCLC samples point to the involvement of many regulatory mechanisms in NSCLC. The expression levels of these targets did not significantly correlate with the pathological stages of NSCLC, according to a core target cancer stage plot analysis with a p-value greater than 0.05 (Figure 7B). Furthermore, the predictive importance of these targets was evaluated. In patients with non-small cell lung cancer (NSCLC), overexpression of PTGS2 was significantly linked to a worse prognosis and a lower overall survival (OS) among the ten key targets (p-value = 0.029) (Figure 8A). Nonetheless, there was a strong correlation between core targets and poorer DFS results in individuals with NSCLC (Figure 8B).

Network pharmacology has created new opportunities for creative approaches to drug development and discovery. This field's fundamental techniques include building and evaluating

drug–gene–disease interaction networks, anticipating drug functionalities for certain diseases, discovering novel drug targets, predicting disease-associated genes, and creating interaction networks for herbal remedies. These methods offer insights into the underlying molecular pathways and make it possible to identify new treatment targets (Zhao et al., 2023).

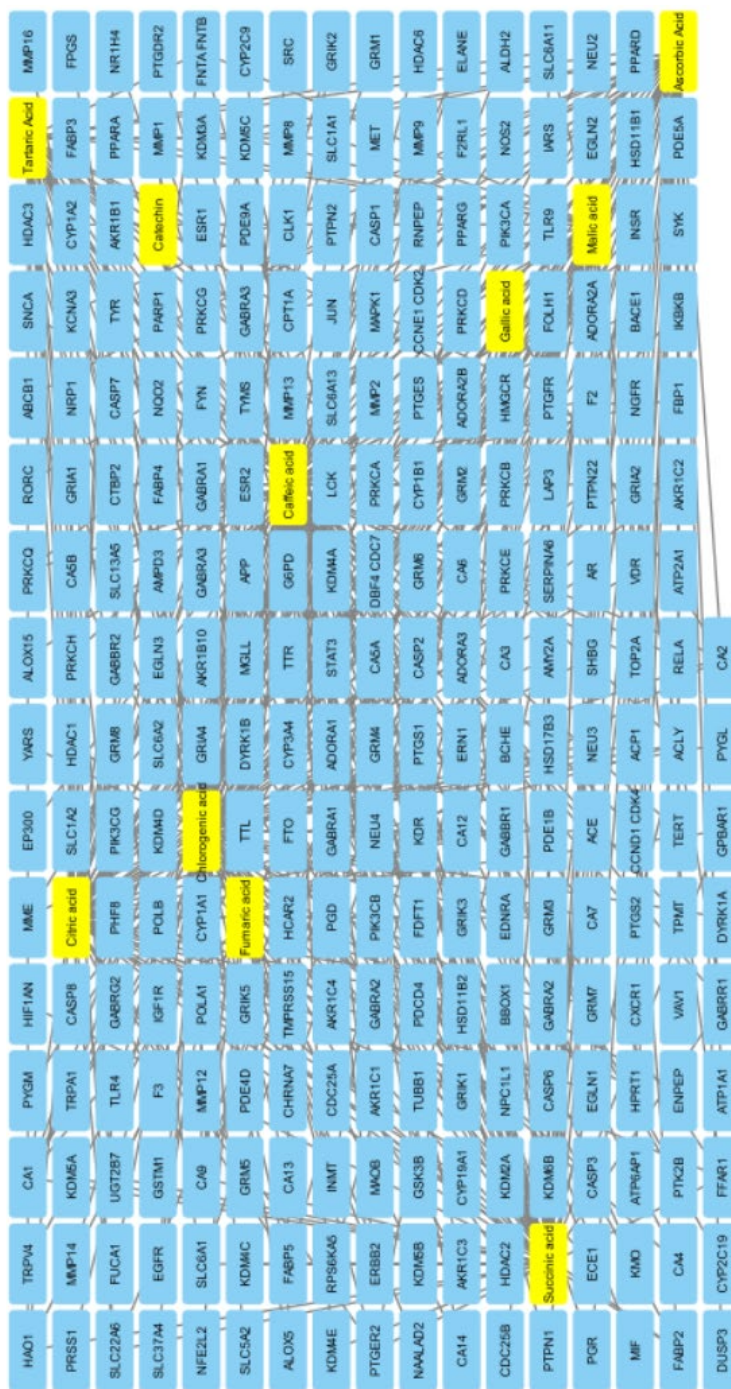
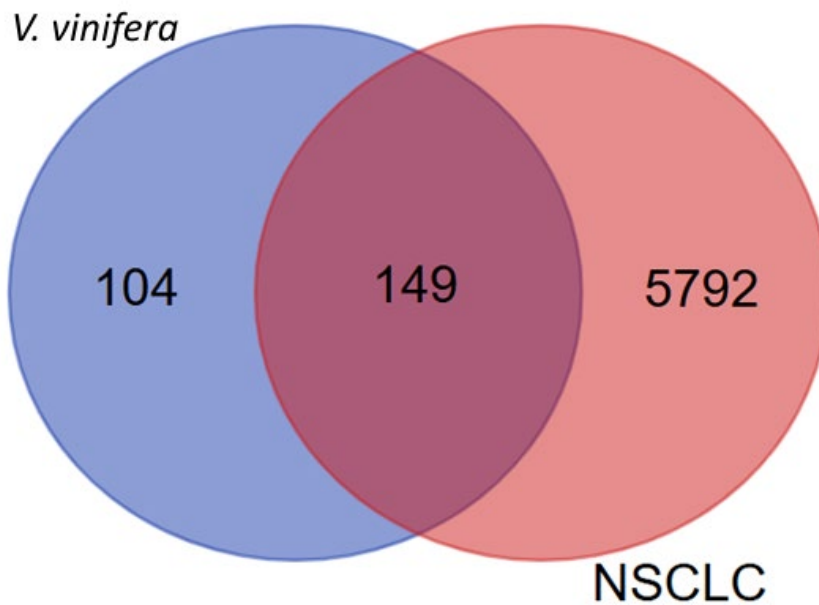


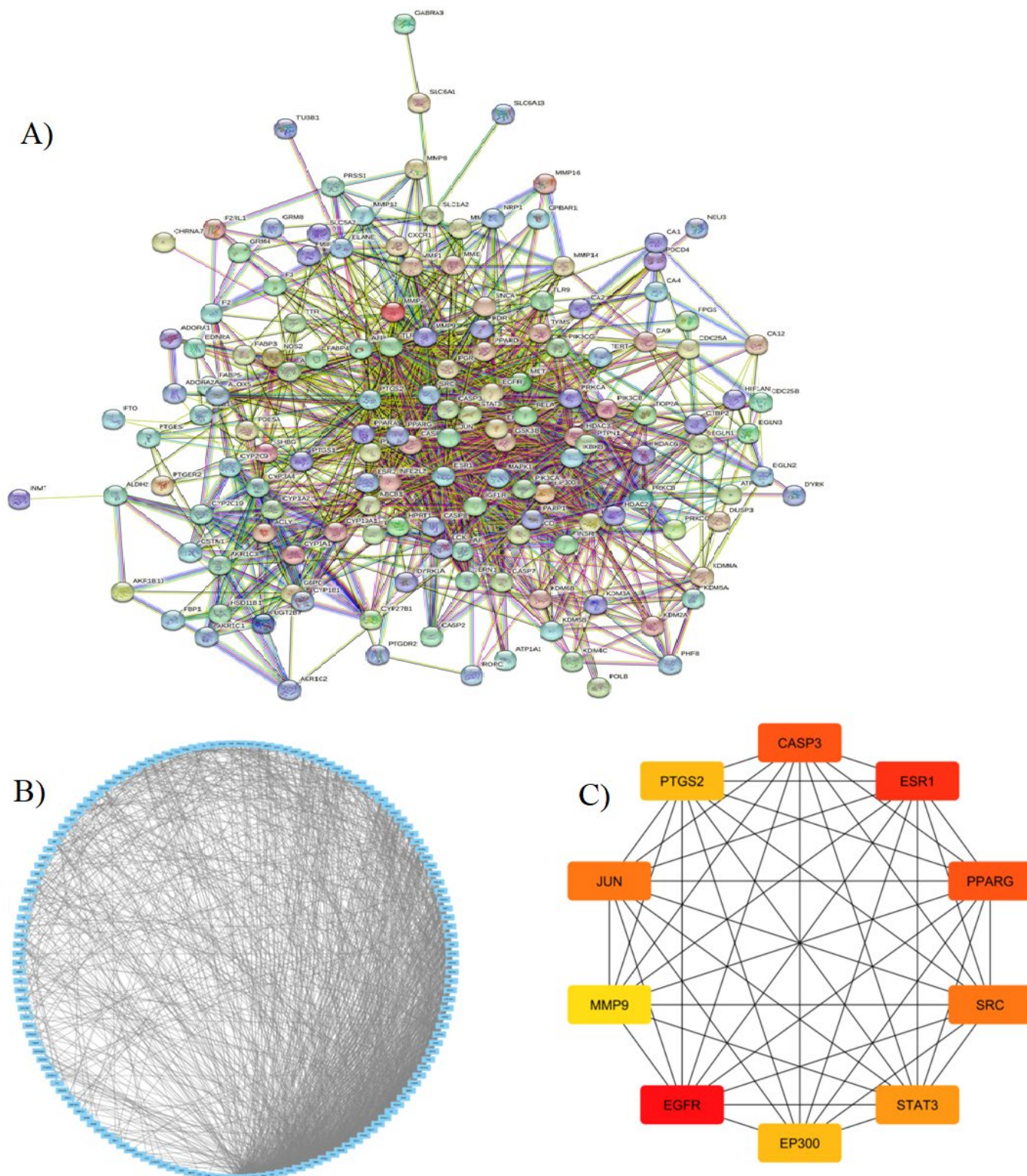
Figure 1. The Drug-target network graph



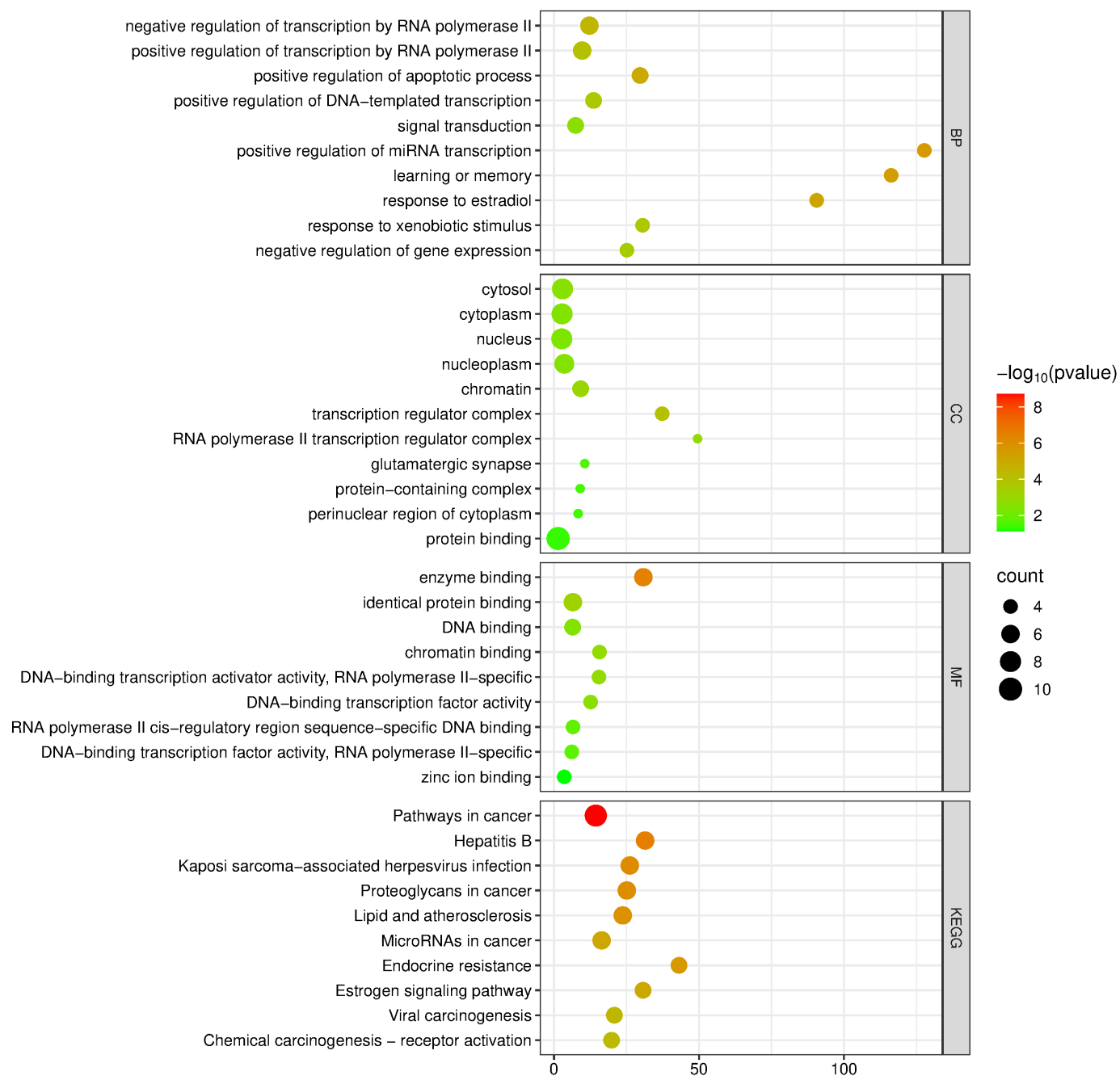
**Figure 2.** Venn diagram of *V. vinifera* (blue) and NSCLC (red) gene targets

**Table 2.** Top 10 key gene targets of grapes' bioactive ingredients

| Rank | Name         | Score |
|------|--------------|-------|
| 1    | <i>EGFR</i>  | 73    |
| 2    | <i>ESR1</i>  | 66    |
| 3    | <i>CASP3</i> | 64    |
| 4    | <i>PPARG</i> | 64    |
| 5    | <i>JUN</i>   | 63    |
| 6    | <i>SRC</i>   | 63    |
| 7    | <i>STAT3</i> | 62    |
| 8    | <i>EP300</i> | 55    |
| 9    | <i>PTGS2</i> | 55    |
| 10   | <i>MMP9</i>  | 53    |



**Figure 3.** PPI analysis. A-B) The PPI network was built using a String database and circular representation using Cytoscape software. C) top 10 core targets ranked by degree method using Cytoscape. Proteins are shown as nodes (colours ranging from red to yellow indicate the degree of interaction amongst anti-NSCLC targets). Edges reflect protein–protein interactions



**Figure 4.** Results of the GO and KEGG pathway enrichment analyses for target proteins interacting with the active compounds are presented. In the GO analysis, the y-axis represents terms for biological processes, cellular components, and molecular functions, while the x-axis indicates the enrichment level. Dot size reflects the number of genes involved, with larger dots corresponding to higher gene counts. For the KEGG analysis, the y-axis lists pathway names, and the x-axis shows the number of genes enriched in each pathway.

**Table 3.** Molecular docking results of the five main active compounds of *V. vinifera* with the top two anti-NSCLC core targets

| Compounds               | PubChem ID | Docking results (kcal/mol) |             |              |
|-------------------------|------------|----------------------------|-------------|--------------|
|                         |            | <i>ESR1</i>                | <i>EGFR</i> | <i>CASP3</i> |
| <b>Caffeic acid</b>     | 689043     | -6.05                      | -7.81       | -5.68        |
| <b>Chlorogenic acid</b> | 1794427    | -6.85                      | -9.01       | -5.91        |
| <b>Citric acid</b>      | 311        | -4.50                      | -10.75      | -4.81        |
| <b>Succinic acid</b>    | 1110       | -4.60                      | -9.35       | -4.18        |
| <b>Ascorbic Acid</b>    | 54670067   | -5.69                      | -5.51       | -4.36        |

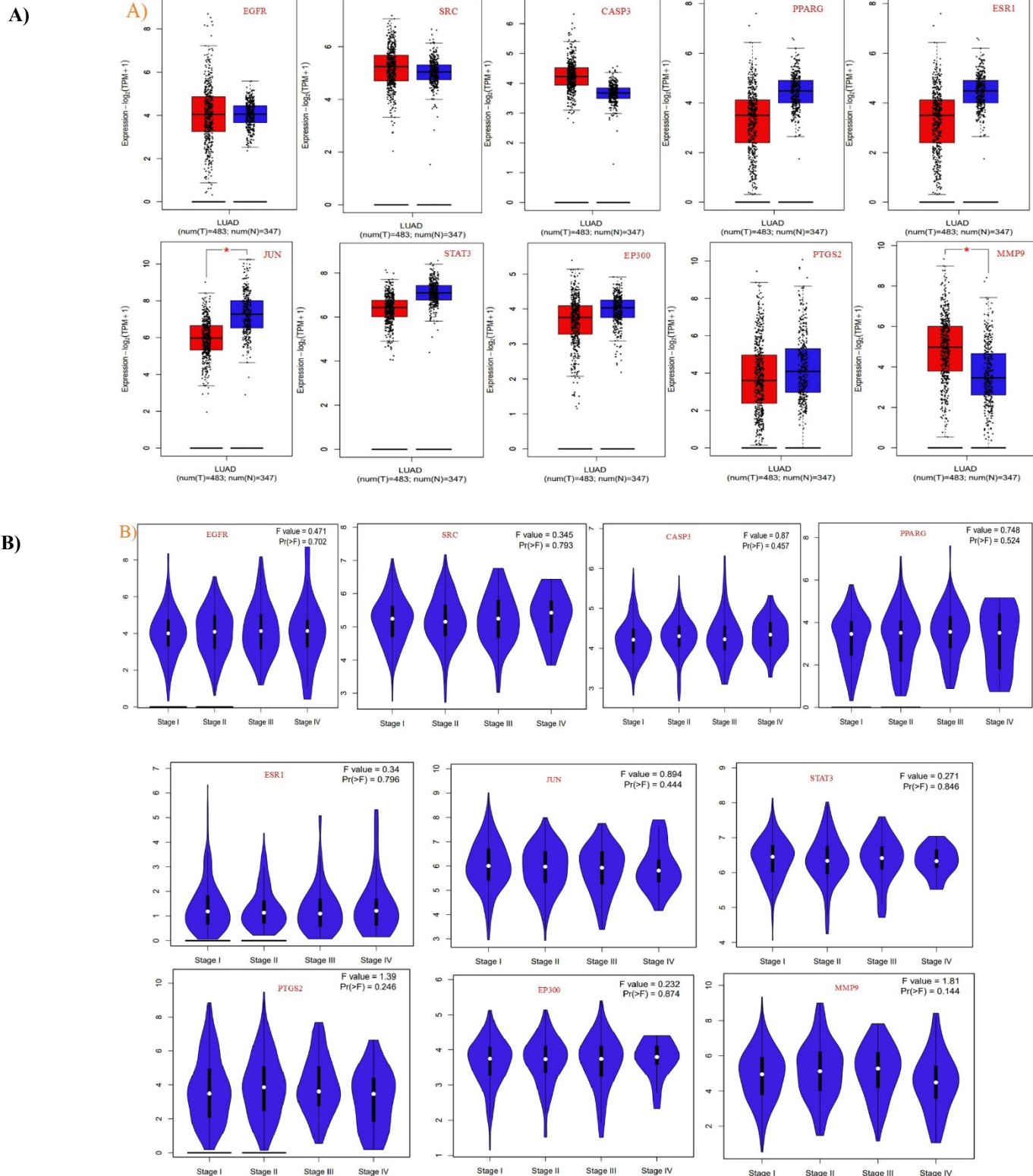
In this study, an integrated network pharmacology and molecular docking approach was employed to provide a comprehensive and systematic investigation into the pharmacological mechanisms of *V. vinifera* bioactive compounds against NSCLC. By evaluating the synergistic potential of ten specific phytochemicals and their interaction with 149 overlapping targets, this research builds upon existing knowledge to offer a more detailed molecular insight into the anti-cancer properties of grape-derived metabolites. Ten *V. vinifera* chemicals were chosen based on biochemical diversity assessments across different grape varieties. 253 distinct possible targets were found using target prediction utilising the Swiss Target Prediction technology. In the meantime, 5,941 possible targets linked to NSCLC were found in the Gene Cards database. The NSCLC-associated and *V. vinifera*-associated target sets had 149 overlapping targets, according to intersection analysis.

Figure 3 A and 3C show the PPI network analysis for intersecting targets as well as the degree of connection between the top 10 targets implicated in the anti-NSCLC activities of *V. vinifera*'s bioactive chemicals, which include *EGFR*, *ESR1*, *CASP3*, *PPARG*, *JUN*, *SRC*, *STAT3*, *EP300*, *PTGS2*, and *MMP9*. These genes could contribute significantly to NSCLC cell proliferation, migration, and apoptosis. For example, the transmembrane receptor *EGFR* causes dimerisation and ATP-dependent autophosphorylation in lung cancer by binding overexpressed ligands such as amphiregulin and *EGF*. Tumour growth, survival, and metastasis are encouraged by this activation of downstream pathways, including mTOR. Aggressive NSCLC development, a poor prognosis, and decreased survival are all correlated with ligand overexpression (T.-C. Liu et al., 2017; Passaro et al., 2020). *ESR1* may also have a role as a prognostic biomarker and therapeutic target in conjunction with ER inhibition in NSCLC, as it is associated with a greater frequency of adenocarcinoma, increased *EGFR/KRAS* mutations, activation of the *MAPK* pathway, and longer overall survival (Hsu et al., 2024). Moreover, *SRC* stimulates tumour

growth, migration, and angiogenesis in NSCLC, and its increased expression is connected to the advancement of the malignancy (Giaccone & Zucali, 2008). It has also been revealed that overactivation of c-FOS/c-Jun in NSCLC is associated with a bigger tumour size, a more aggressive tumour histotype, and an increased risk of metastasis (Manios et al., 2024).

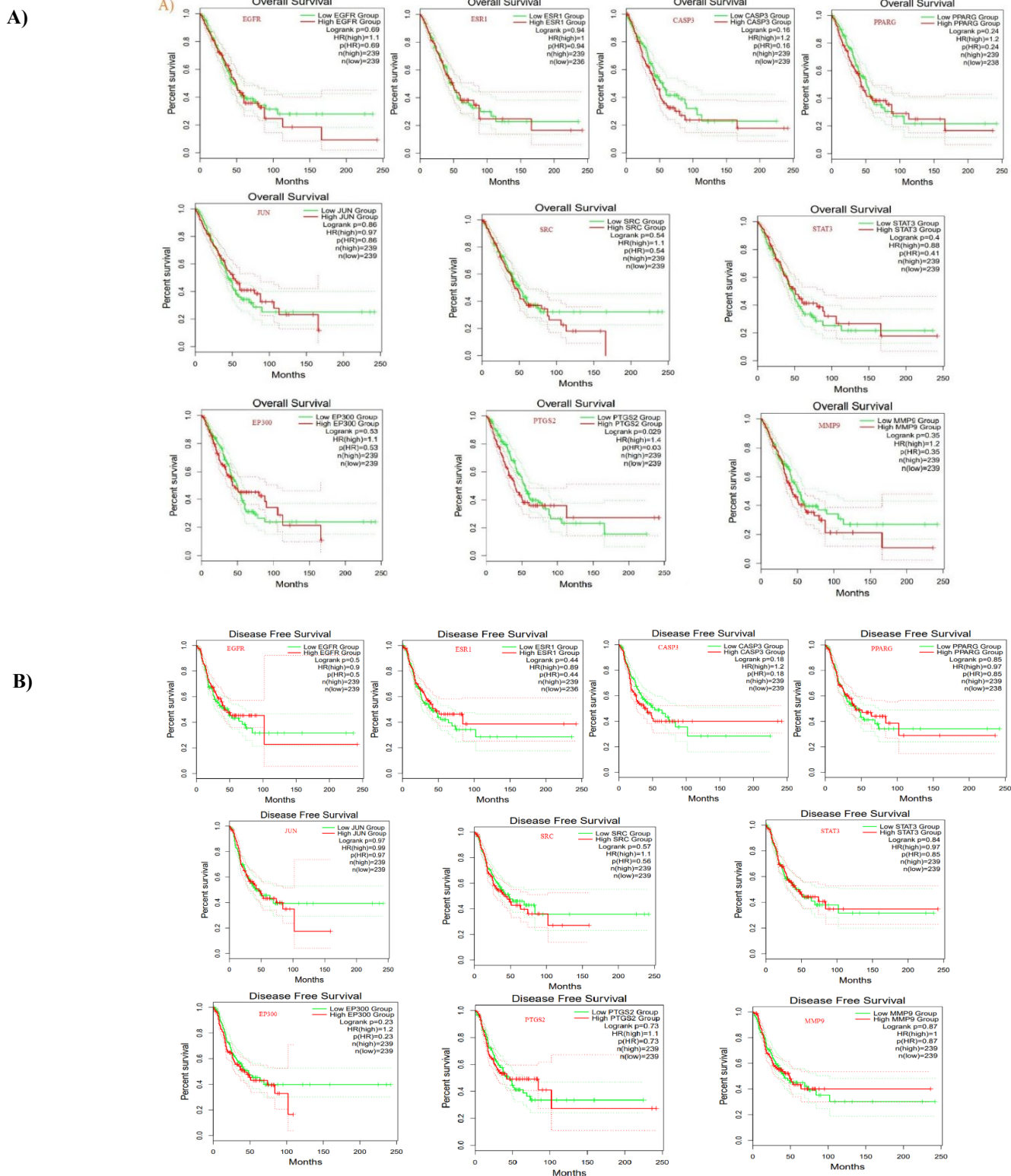
The *V. vinifera* target genes for NSCLC treatment were leveraged to construct an enrichment map of GO and KEGG pathways using the David online database (Figure 4). *FAA* revealed its anti-HCC technique by modulating gene targets involved in BP, such as RNA polymerase II's negative regulation of transcription, RNA polymerase II's positive regulation of transcription, the positive regulation of the apoptotic process, signal transduction and so on, as indicated in Figure 4. Dysregulation of RNA polymerase II transcription in cancer through altered initiation, elongation, or pausing drives aberrant gene expression and carcinogenesis. Transcription factor II-I, a key regulator capable of activating or repressing transcription, is often misregulated in cancer. This transcriptional dependence renders tumours vulnerable to inhibitors targeting transcriptional kinases and associated proteins (Linzer et al., 2021; Vervoort et al., 2022). Furthermore, through the interaction of autophagy and signalling pathways, including p53, mTOR/PI3K-Akt, and the Bcl-2 family, apoptosis regulation in NSCLC delicately balances tumour suppression and survival (G. Liu et al., 2017). Some KEGG pathways included pathways in cancer, lipid, arteriosclerosis and proteoglycans in cancer. It is the case of signalling pathways such as *RAS-RAF-MEK-ERK* and *PI3K-Akt*, which are frequently triggered by *EGFR*, promote cell survival, proliferation, resistance to apoptosis, and resistance to chemotherapy in NSCLC (Alam et al., 2023; Liu et al., 2025). Moreover, through their ability to modify the tumour stroma and change connections between cells and the matrix, proteoglycans influence tumour development, metastasis, angiogenesis, treatment resistance, and cell signalling (Ahrens et al., 2020; Theocharis & Karamanos, 2019).





**Figure 7.** Expression of the top ten anti-NSCLC/LUAD core targets in NSCLC and pathological phases.

A) Expression of the 10 key target genes in NSCLC/LUAD (the red and blue boxes indicate tumour and normal cells, respectively). B) Correlation between core target gene expression levels and NSCLC/LUAD pathological stages using TCGA data.



**Figure 8.** The relationship between core target gene expression and prognosis in patients with NSCLC/LUAD tumours. There was a strong link between increased gene expression and overall survival (A) and disease-free survival (B) of patients with tumours

Molecular docking was used to examine *V. vinifera*'s inhibitory effects on important anti-NSCLC targets in order to determine its anticancer potential against NSCLC. In particular, three main targets, *EGFR*, *ESR1*, and *CASP3*, were docked with five important compounds: ascorbic acid, citric acid, succinic acid, chlorogenic acid, and caffeic acid. Strong binding affinities were found in the findings; the complexes, including succinic acid, citric acid, and chlorogenic acid, had the highest affinities. These protein–ligand complexes also showed stability, with at least two hydrogen bonds supporting each one. Notably, a large body of research emphasises how important hydrogen bonds are for molecular recognition and preserving the stability of protein–ligand complexes (Hubbard, 2001).

On the other hand, the majority of important targets had differential expression between NSCLC and normal tissues, according to an analysis of the *GEPIA2* database results. Only *PTGS2* overexpression was associated with a poor prognosis and a lower overall survival rate among them (Figures 7 and 8). These results imply that these key targets could have a major impact on the development of NSCLC and are excellent candidates for treatment using chemicals from *V. vinifera*.

## Conclusion

The anticancer potential of the phytochemicals from *V. vinifera* was investigated in this study using an integrated network pharmacology and molecular docking method against NSCLC. Numerous biological processes and signalling pathways were found to be involved in the therapeutic effects of *V. vinifera*. These included RNA polymerase II's positive and negative regulation of transcription, the promotion of apoptotic processes, signal transduction, cancer-related pathways, lipid and atherosclerosis pathways, and proteoglycan signalling in cancer. According to molecular docking analysis, the five phytochemicals had substantial binding affinities with important oncogenic targets, including *ESR1*, *EGFR*, and *CASP3*, indicating that they may be used as multi-target inhibitors in the treatment of NSCLC. The results show that *V. vinifera* phytoconstituents are viable options for treating NSCLC. Future investigations should explore the potential synergistic or additive effects of combining multiple grape-derived compounds, as traditional medicinal formulations often rely on multi-component interactions rather than single isolated agents. However, thorough *in vitro*, *in vivo*, and clinical studies are necessary to confirm their safety and therapeutic effectiveness for possible clinical use.

## Compliance with Ethical Standards

**Conflict of interest:** The author(s) declare that they have no actual, potential, or perceived conflicts of interest related to this article.

**Ethics committee approval:** Ethics committee approval is not required for this study.

**Data availability:** The data that has been used is confidential

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