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Original Article

Exploring the Mechanism of Isoliquiritigenin on Lung Cancer Based on Network Pharmacology and Molecular Docking

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ABSTRACT

Objectives: This study aims to explore how Isoliquiritigenin (ISL) combats lung cancer by using network pharmacology and molecular docking techniques. **Materials and Methods:** We used multiple databases to find ISL-related targets and lung cancer-associated genes, followed by enrichment analysis using the Cluster Profiler package. Network analysis via the STRING database and Cytoscape illuminated the protein-protein interaction landscape. The Kaplan-Meier plotter evaluated the prognostic relevance of gene expression. Molecular docking assessed the binding affinity of ISL to key proteins. **Results:** Our study identified 412 ISL targets and intersected these with 15,373 lung cancer-related genes, pinpointing 232 genes of potential therapeutic interest. Enrichment analysis revealed significant pathways, including those related to cancer and cellular signaling. Network analysis underscored key nodes such as AKT1, TNF, EGFR, HSP90AA1 and ESR1. Molecular docking confirmed substantial binding affinities, suggesting inhibitory capabilities against these proteins. **Discussion:** The enrichment analysis implicated ISL in modulating a spectrum of biological processes, particularly those involved in cell communication and systemic biological functions. Key genes identified via network analysis could serve as novel targets for intervention. Molecular docking emphasized ISL's potential as a multi-target inhibitor, thus reinforcing its candidacy as a promising therapeutic agent against lung cancer.

Keywords: ISL, Isoliquiritigenin, Lung Cancer, Molecular Docking, Network Pharmacology, Protein-Protein Interactions.

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INTRODUCTION

Lung cancer remains a major cause of cancer-related deaths globally, posing a serious public health issue worsened by high illness and death rates.[1,2] Although there have been great advances in the diagnosis and treatment of lung cancer, the survival rate for patients in advanced stages is still very low.[3,4] The development of lung cancer is linked to many factors, including genetic mutations, epigenetic changes and environmental influences, which make it difficult to detect and treat.[5,6] Because of the complexity and drug resistance of lung cancer, traditional lung cancer treatments often fail to work. This has led to an urgent need for new treatments.[7,8]

Isoliquiritigenin (ISL) is a flavonoid compound found in licorice root, which has attracted much attention due to its significant anti-inflammatory, antioxidant and anticancer effects.[9-11] Studies have found that ISL is involved in several signaling pathways related to cell growth, apoptosis and cancer metastasis.[12,13] Therefore, we urgently need innovative treatments that can target lung cancer. In this study, a comprehensive network pharmacology approach combined with molecular docking technology was used to systematically explore the molecular targets of ISL in lung cancer to fill this gap. By integrating and analyzing data from different sources, we aim to elucidate the molecular interactions between ISL and genes associated with lung cancer, thereby screening possible key pathways and genes to provide viable targets for lung cancer treatment. This is very important for understanding ISL as a potential drug for the treatment of lung cancer and can serve as a basis for further research to provide new directions and ideas for the treatment of lung cancer. Natural Chinese herbal medicine provides a new therapeutic prospect for tumor therapy; ISL has a wide range of biological activities and has the value of further research and development. Through network pharmacology and molecular docking, this study aims to explore the possible mechanism of ISL action on lung cancer and identify new therapeutic targets that may act on lung cancer.

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MATERIALS AND METHODS

Acquisition of ISL-Related Targets

To identify ISL's operational targets, we utilized a comprehensive approach from multiple databases, including PubChem,[14] Swiss Target Prediction[15] TCMSP,[16] and Super-PRED.[17] The targets identified from these databases were merged. Subsequently, an ID conversion process using the UniProt database was performed to ensure the uniformity of the gene or protein identifiers.[18] This approach facilitated the compilation of a comprehensive list of potential targets, which was subsequently deduplicated to obtain a distinct set of ISL-related targets.

Acquisition of Lung Cancer-Related Genes

In order to identify genes associated with lung cancer, an extensive search was performed across three databases: DisGeNET, MalaCards and GeneCards.[19-21] The aggregated lung cancer-related genes from various databases were compiled into a collective dataset. This dataset underwent a deduplication process, which ensured only unique gene entries remained, removing any redundant data. The final list was then intersected with the ISL-related targets identified earlier, revealing the specific genes that ISL might modulate in lung cancer.

Enrichment Analysis Using ClusterProfiler

Enrichment analysis was performed using the ClusterProfiler package in R to identify significant biological processes, molecular functions, cellular components and pathways associated with the genes of interest.[22] The analysis parameters were set with a method for adjusting *p*-values (pAdjustMethod) as "BH" for Benjamini-Hochberg and a q-value cutoff threshold of 0.05 to determine significance. This methodological framework allowed for the robust identification of statistically overrepresented categories in the gene set, minimizing the rate of false positives due to multiple comparisons.

Network Analysis of ISL-Related Genes in Lung Cancer

The potential genes related to the effects of ISL on lung cancer were analyzed for Protein-Protein Interactions (PPIs) using the STRING database.[23] The resulting interaction data were then visualized using the Cytoscape software, providing a graphical representation of the molecular interactions.[24] Network parameters for each gene, particularly the degree of connectivity within the network, were computed using the CentiScape plugin for Cytoscape.[25] This plugin calculates various centrality measures that describe the importance of a node within a network, with degree centrality reflecting the number of connections a node has to other nodes.

Kaplan-Meier Plotter Analysis

This study utilized the Kaplan-Meier Plotter tool to create survival plots. This online database assesses the impact of different genes on the survival of cancer patients.[26] Patient cohorts were divided based on the expression levels of four genes: AKT1, HSP90AA1, EGFR and ESR1 to create survival plots. Expression levels were categorized into high and low groups, based on the median expression levels within the patient population. Hazard Ratios (HR), 95% confidence intervals and logrank *p*-values were calculated to determine the significance of survival differences between high and low groups. The number of patients at risk was shown at various time intervals to give an idea of the sample size throughout the follow-up period.2.6 Molecular docking.

The 3D protein structure of the core target was retrieved from the RCSB Protein Data Bank (RCSB PDB, http://www.pdb.org/) and subsequently segmented using PyMOL software.[27,28] The 3D structure of ISL was obtained from PubChem. Docking experiments between the core component and the core target were conducted utilizing AutoDock Vina software.[29] Stable binding sites were determined based on a binding energy threshold of ≤-5.0 kcal/mol.

RESULTS

ISL-related targets

After the database search and ID conversion, we identified a total of 412 ISL-related targets.

ISL Targets in Lung Cancer

Combining lung cancer related genes from several database, a total of 15,373 lung cancer related genes were obtained after replication. These genes were intersected with 412 ISL-related targets to identify 232 genes in which ISL acts on lung cancer (Figure 1).

Cluster Profiler Enrichment Analysis Results

The results of GO and KEGG enrichment analysis of the above 232 genes using the ClusterProfiler package showed that the G protein-coupled receptor signaling pathway, vascular processes within the circulatory system and regulation of trans-synaptic signaling were significantly enriched. In the Cellular Component (CC) category, there is notable enrichment in areas such as the neuronal cell body, synaptic membranes and cytoplasmic vesicle lumen. Molecular Function (MF) was enriched to G protein-coupled amine receptor activity, neurotransmitter receptor activity and p53 binding. KEGG enrichment analysis showed significant enrichment of synapses, including neuroactive ligand-receptor interactions, calcium signaling pathways and cancer pathways, especially prostate cancer, cancer proteoglycan and serotonergic pathways, as shown in Figure 2.

Of key genes

Analysis of the protein-protein interaction network, shown in Figure 3, reveals complex interactions between genes that may be affected by ISL in lung cancer. Using the CentiScape 2.0 plug-in, we found several highly centralised genes, suggesting that they play an important role in the network. Specifically, genes such as AKT1, TNF, EGFR, HSP90AA1 and ESR1 become central nodes with extensive connections to other genes. Their central nature highlights their possible important role in lung cancer, as well as a promising target for the therapeutic effects of ISL. The network analysis not only highlighted the critical role of these genes, but also suggested possible multifaceted mechanisms of action for ISL, providing insights into its Potential efficacy in treating lung cancer.

Prognostic Value of Gene Expression Levels in Cancer Survival Identified through Kaplan-Meier Plots

The relationship between different gene expression levels and survival time of patients is shown in Figure 4. For AKT1, the Hazard Ratio (HR) was 1.12 (95% CI: 0.99-1.26), indicating a moderate effect size. Although the *p* value was 0.068, the HR and its confidence interval suggest a trend towards reduced survival with higher AKT1 expression, emphasizing the potential biological relevance despite the lack of conventional statistical significance. This suggests that increased AKT1 expression may reduce the survival rate of patients. High HSP90AA1 expression was associated with significantly lower survival, with a hazard ratio of 1.26 (95% CI: 1.12-1.43) and a P-value of 0.00014. Elevated EGFR and ESR1 levels are associated with better survival outcomes. The Hazard Ratio (HR) for EGFR was 0.8 (95% CI: 0.69-0.92), reflecting a considerable protective effect and survival advantage for patients with high EGFR expression. The *p*-value of 0.0027 reinforces this result, highlighting the clinical relevance of EGFR expression levels. Similarly, ESR1 had a hazard ratio of 0.85 (95% CI: 0.76-0.96) with a *p* value of 0.009.

Molecular docking

The results of molecular docking analysis showed that ISL had significant binding affinity for multiple protein targets, with binding energy scores exceeding the minimum standard of -5.0 kcal/mol. Specifically, ISL interacted with AKT1 at the ATP-binding site through hydrogen bonding and hydrophobic interactions, which could inhibit the kinase activity of AKT1 and disrupt downstream signaling. For TNF, ISL formed stable hydrogen bonds with key residues in the receptor-binding interface, potentially blocking TNF's pro-inflammatory signaling. In the case of EGFR, ISL bound to the tyrosine kinase domain, forming hydrogen bonds and van der Waals interactions that may inhibit EGFR activation and subsequent signaling cascades.

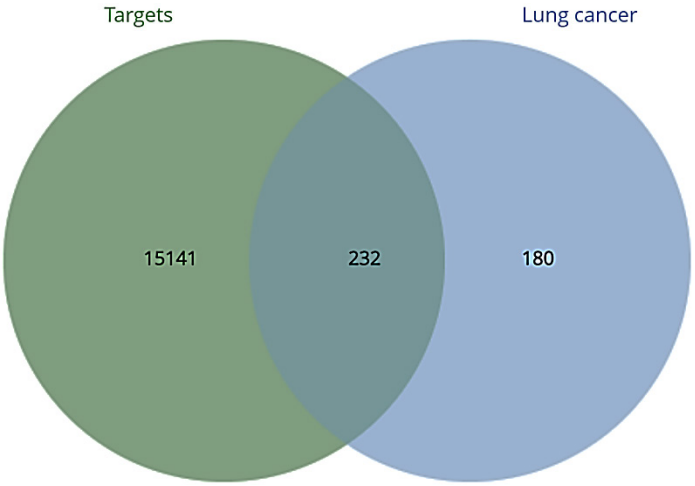

Figure 1: Venn diagram illustrating the overlap between ISL-related genes (green, 15,141) and lung cancer-related genes (blue, 180), with 232 shared genes potentially targeted by ISL in lung cancer.

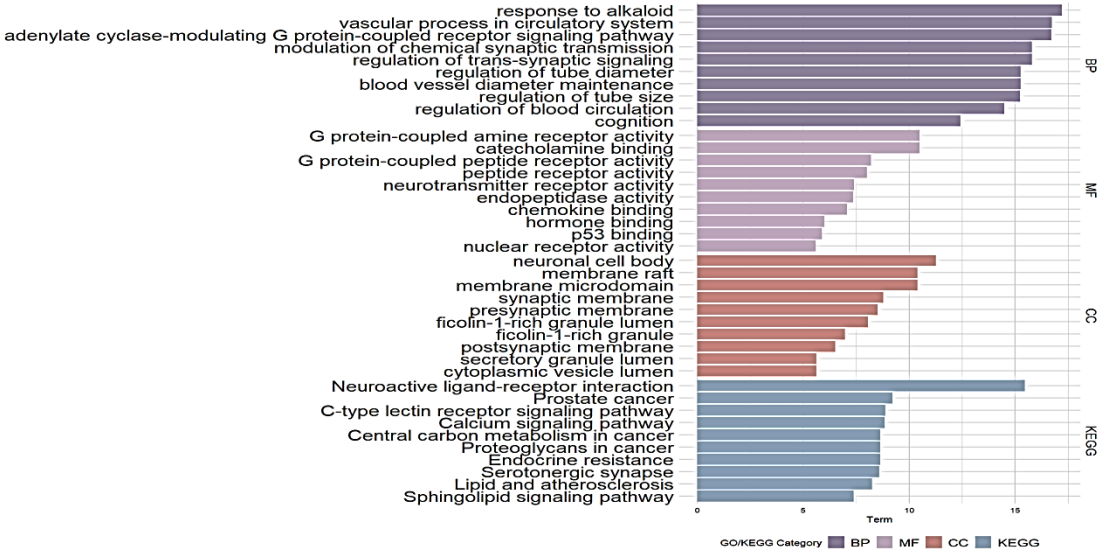

Figure 2: GO and KEGG enrichment analysis of ISL-related genes in lung cancer.

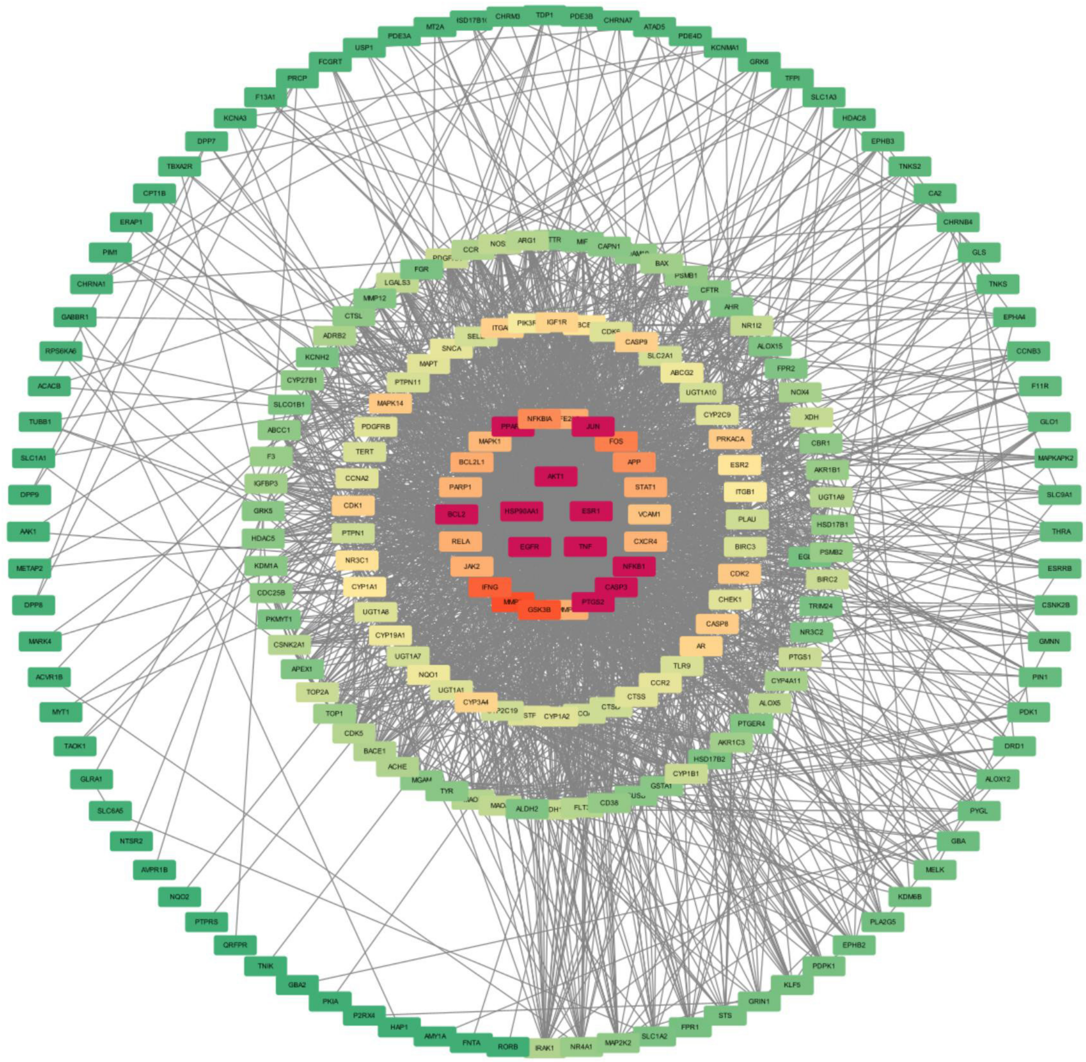

Figure 3: Protein-Protein Interaction (PPI) network of ISL-targeted genes in lung cancer. Nodes closer to the center with deeper red color represent genes with a higher degree of connectivity, indicating central hubs in the network, while nodes with deeper green color on the periphery have a lower degree of connectivity. This visualization highlights key genes, such as AKT1 and EGFR, which play a crucial role in the network.

These specific binding interactions provide mechanistic insights into how ISL may exert its anticancer effects by interfering with critical protein functions in lung cancer. Figures 5A to 5E depict the docking positions of ISL at various protein targets and Figures 5E and 5F show different binding sites on EGFR. These docking results show that ISL plays its role in a series of molecular pathways, indicating that it plays an important role in the development of liver cancer.

DISCUSSION

Exploring the use of ISL in lung cancer pharmacology unveils a complex network of molecular interactions and promising therapeutic pathways. Given its documented efficacy in other cancers such as hepatic and breast cancer, there is a strong foundation for investigating its potential in lung cancer. This research could reveal similar multifaceted biological effects that make ISL an effective anticancer agent.[30,31] We utilized a series of bioinformatics tools to delve deeper into the signaling pathways and physiological processes associated with gene enrichment in lung cancer. The results reveal the possible mechanism by which ISL exerts its anticancer effect. Our discovery of a significant enrichment of the neuroactive ligand-receptor interaction pathway inhibits previous research linking neurotransmitter signaling to the progression of cancers such as breast cancer. This similarity suggests that the expression of neurotransmitter may play a key role in cancer development, and it has been shown that neurotransmitter is generally very prevalent in aggressive cancer types and is known to co-express with neurotransmitter receptors. Our findings once again illustrate the importance of these pathways in carcinogenesis and their potential as targets for therapeutic intervention.[32,33] Our findings suggest that ISL may influence cancer cell communication and potentially alter tumor behavior by modulating neurotransmitter dynamics or receptor activity. In addition, it is worth noting that calcium signaling pathway plays a key role in cell proliferation and apoptosis, which

is consistent with existing research, illustrating the importance of this signaling pathway in tumors and its potential as a new approach to cancer treatment.[34,35]

Our study identified significant enrichment of the G Protein-Coupled Receptor (GPCR) signaling pathway, which is crucial in regulating various cancer-related processes, including cell growth, survival, migration and metastasis. In lung cancer, GPCRs activate key downstream signaling pathways, such as MAPK and PI3K/AKT, which are implicated in tumor progression and therapy resistance. Research has shown that dysregulated GPCR signaling contributes to a pro-tumorigenic microenvironment by promoting angiogenesis, immune evasion and cancer cell invasiveness (Liebmann, 2004; Predescu *et al.*, 2019). Additionally, GPCRs are involved in the modulation of neurotransmitter dynamics, which can influence tumor behavior and are often linked to more aggressive cancer phenotypes. By interfering with these critical pathways, ISL may exert its anticancer effects. These findings highlight the therapeutic potential of targeting GPCR signaling in lung cancer and reinforce our hypothesis with substantial support from existing literature.[36,37] ISL may affect a series of downstream signals related to tumorigenesis by interfering with the potential of this pathway. Network analysis using the STRING database and Cytoscape identified key genes such as AKT1, TNF and EGFR as central hubs in the Protein-Protein Interaction (PPI) network, indicating their pivotal roles in lung cancer progression. AKT1 is a crucial component of the PI3K/AKT signaling pathway, which regulates cell proliferation, survival and metabolism. Aberrant activation of AKT1 is associated with enhanced tumor growth and resistance to apoptosis in lung cancer. TNF is a pro-inflammatory cytokine that can have dual effects on cancer; it promotes tumor cell death through apoptosis but may also contribute to tumor progression

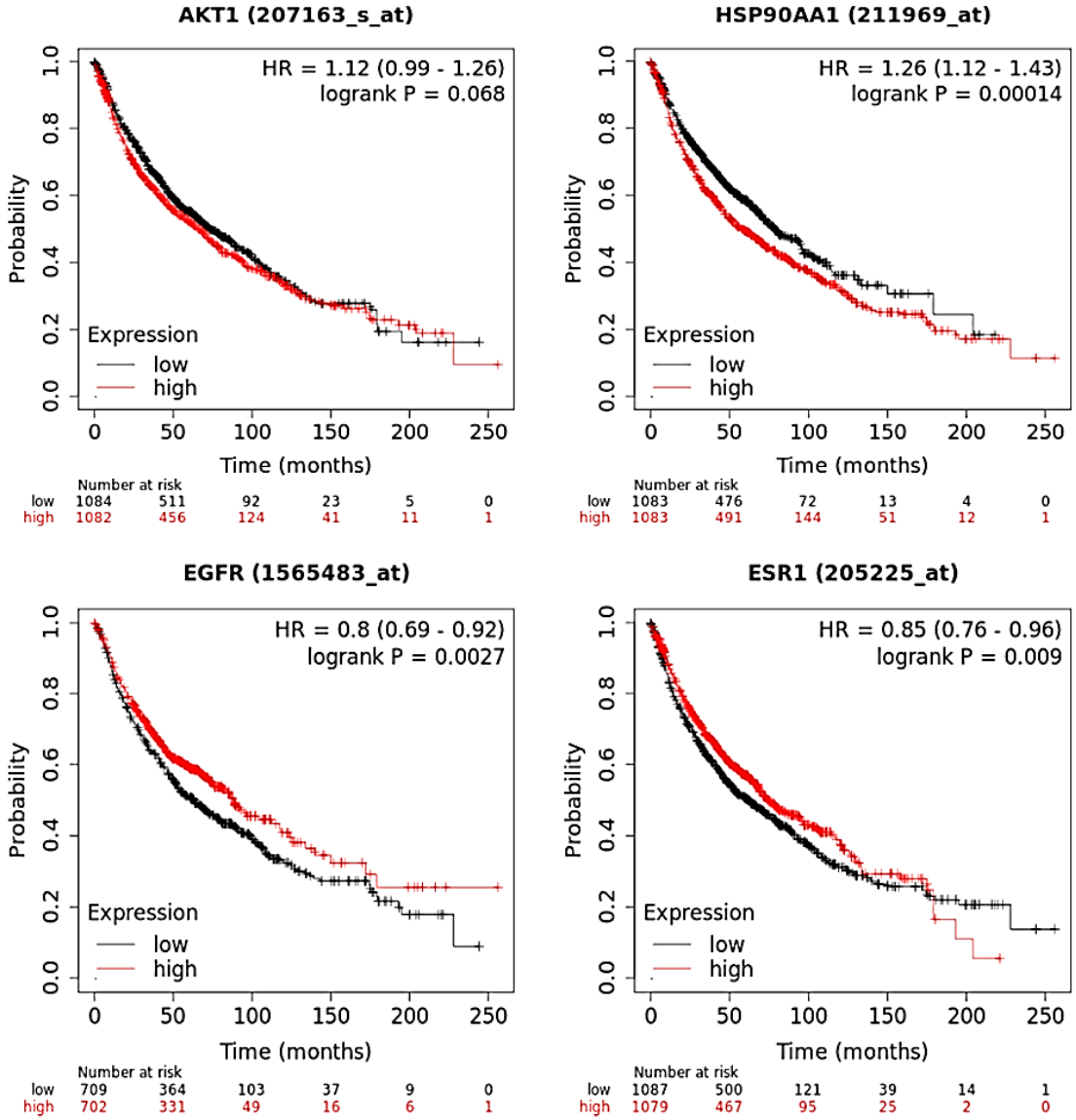

Figure 4: Kaplan-Meier Analysis of Gene Expression and Cancer Patient Survival.

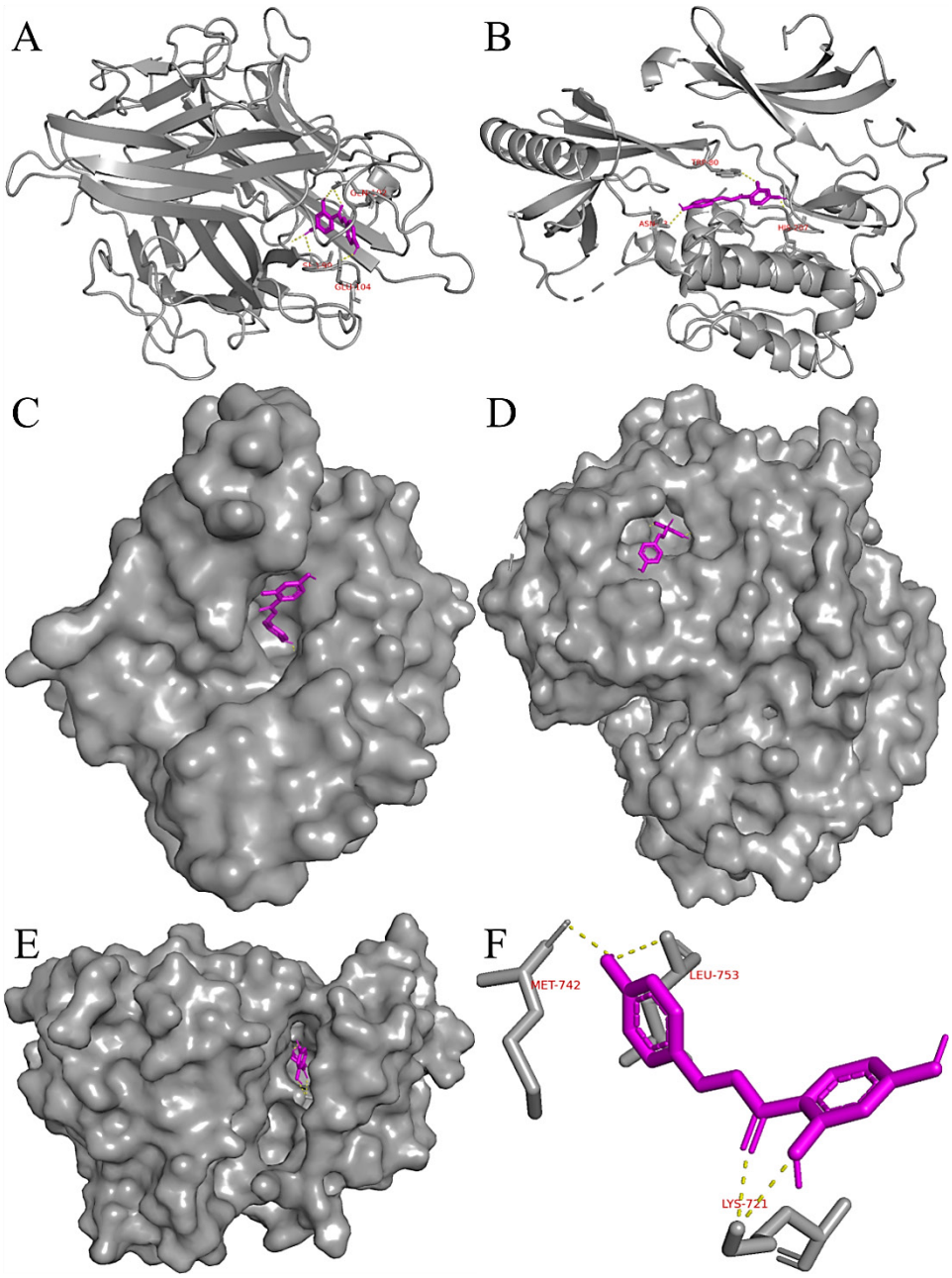

Figure 5: Molecular docking results of ISL with key genes, (A) AKT1, (B) TNF, (C) HSP90AA1, (D) ESR1, (E, F) Binding interactions with EGFR.

by creating a pro-tumorigenic inflammatory microenvironment. EGFR, a well-known receptor tyrosine kinase, is frequently mutated or overexpressed in lung cancer, driving cell proliferation and survival through pathways such as RAS/RAF/MEK/ERK and PI3K/AKT. The central roles of these genes in cancer-related signaling pathways suggest that ISL may exert its therapeutic effects by modulating these critical molecular mechanisms. These analytical results are consistent with molecular docking results, which show strong binding affinity of ISL to these central proteins and hypothesize its inhibitory potential to block cancer-promoting pathways. Binding interactions with key targets such as EGFR and AKT1 play an important role in the oncogenic signaling network, illustrating the possible role of ISL as a molecular antagonist and providing a practical mechanism for its preclinical action. The binding energy of ISL was significantly lower than the -5.0 kcal·mol^{-1} threshold. This suggests that ISL may exert its anticancer effects by inhibiting kinase activity and interfering with essential proteins such as heat shock proteins and estrogen receptors that are essential for cancer cell proliferation and survival. This is consistent with the findings of other studies in the literature.[38,39]

CONCLUSION

Together, our study highlights the potential of ISL as a multifaceted anticancer agent, particularly for lung cancer. Integrating network pharmacology and molecular docking studies, we elucidate several key pathways and genes of ISL, such as the neuroactive ligand-receptor interaction pathway, calcium signaling pathway and G protein-coupled receptor signaling pathway. These pathways play an important role in the regulation of cell proliferation, apoptosis and cancer progression. The ability of ISL to disrupt key signaling networks in cancer cells is highlighted, suggesting its role as a potent inhibitor of tumorigenesis. In addition, the strong binding affinity of ISL to central proteins such as EGFR and AKT1 suggests its potential to block cancer-promoting pathways, providing a promising mechanism for its therapeutic effect. This comprehensive analysis provides a theoretical basis for the treatment of lung cancer and potentially other aggressive cancers with ISL.

Despite the promising findings of this study, there are several limitations that must be acknowledged. Firstly, our research is based solely on *in vitro* experiments and molecular docking analyses, which provide initial insights into the potential mechanisms of ISL but do not fully represent the complexity of biological systems *in vivo*. Without *in vivo* validation, it is difficult to confirm the therapeutic efficacy and safety of ISL in a whole-organism context. Additionally, molecular docking studies, while useful for predicting protein-ligand interactions, may not always accurately reflect the dynamic nature of protein binding in a living system. Future research should aim to conduct *in vivo* studies and clinical trials to validate these findings and explore the pharmacokinetics and pharmacodynamics of ISL in lung cancer models. This will provide a more comprehensive understanding of ISL's potential as a therapeutic agent and help bridge the gap between experimental research and clinical application.

ACKNOWLEDGEMENT

None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ISL: Isoliquiritigenin; **PPIs:** Protein-protein interactions; **HR:** Hazard ratios; **CC:** Cellular Component; **MF:** Molecular function; **GPCR:** G protein-coupled receptor.

SUMMARY

In Summary, our study highlights the potential of ISL as a multifaceted anticancer agent, particularly for lung cancer. Integrating network pharmacology and molecular docking studies, we elucidate several key pathways and genes of ISL, such as the neuroactive ligand-receptor interaction pathway, calcium signaling pathway and G protein-coupled receptor signaling pathway. These pathways play an important role in the regulation of cell proliferation, apoptosis and cancer progression. The ability of ISL to disrupt key signaling networks in cancer cells is highlighted, suggesting its role as a potent inhibitor of tumorigenesis. In addition, the strong binding affinity of ISL to central proteins such as EGFR and AKT1 suggests its potential to block cancer-promoting: pathways, providing a promising mechanism for its therapeutic effect. This comprehensive analysis provides a theoretical basis for the treatment of lung cancer and potentially other aggressive cancers with ISL.

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