

Network Pharmacology-Based Elucidation of Piperlongumine Action on Oncogenic Survival and Immune-Evasive Pathways in Pancreatic Cancer

Imene Derardja^{1,2}, Redouane Rebai^{1,3}, Luc Jasmin⁵, Abdennacer Boudah³

¹. Department of biology, Faculty of natural life science, earth and universe sciences, Mohamed Khider University Biskra, Algeria

². Laboratory Promotion of Innovation in Agriculture in Arid Regions (PIARA), Mohamed Khider University, PO Box 145 RP, 07000 Biskra, Algeria

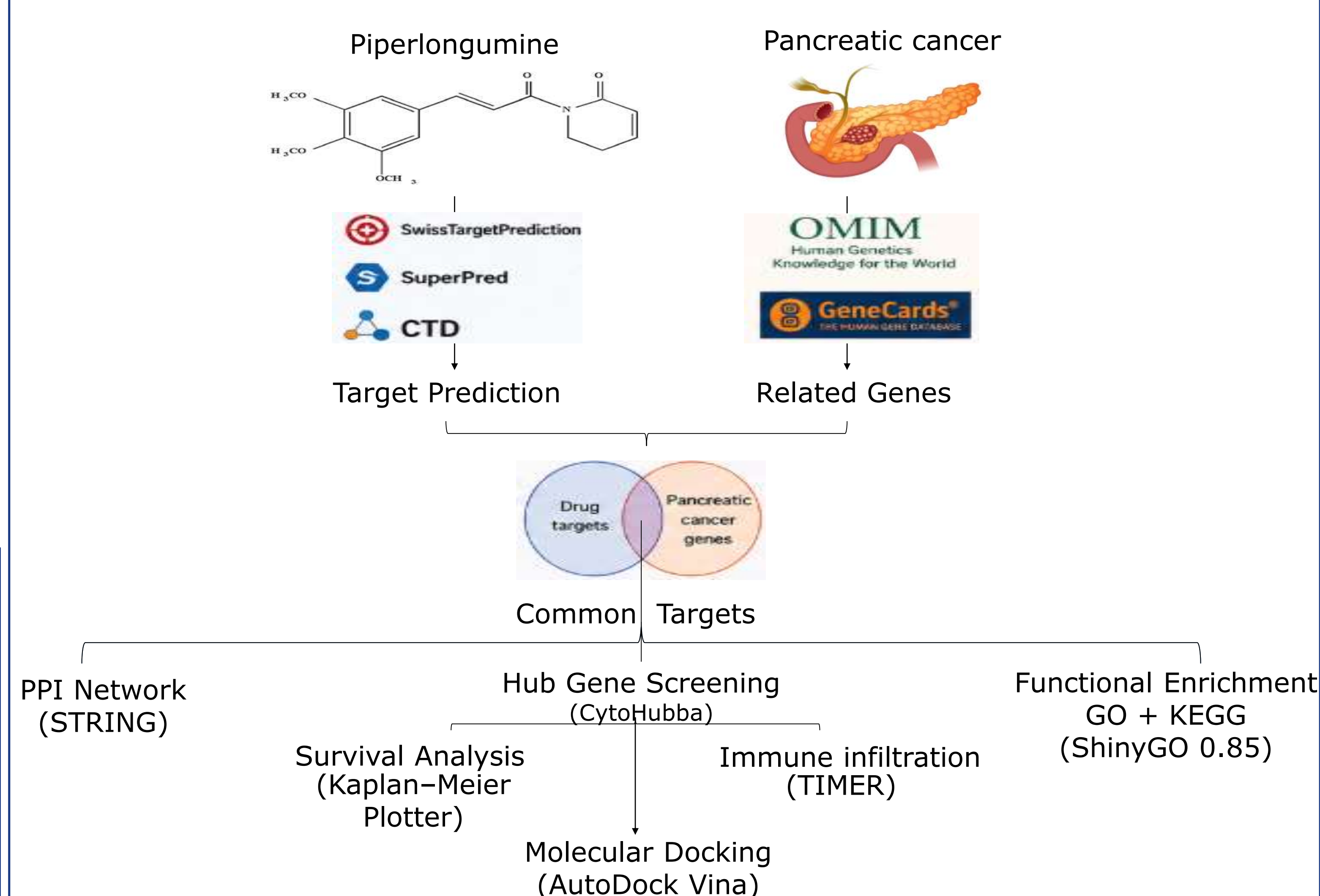
³. Laboratory of Biotechnology, National Higher School of Biotechnology, Constantine 25000, Algeria

⁴. Department of Oral and Maxillofacial Surgery, University of California, San Francisco, 707 Parnassus Ave Suite D-1201, San Francisco, CA, 94143, USA

INTRODUCTION & AIM

Pancreatic cancer remains one of the most lethal malignancies, characterized by late diagnosis, poor prognosis, and limited therapeutic options. Conventional chemotherapeutic strategies are often associated with high systemic toxicity and insufficient selectivity, leading to significant damage to normal tissues while offering only modest survival benefits. These limitations highlight the urgent need for alternative anticancer agents with improved efficacy and tumor selectivity. Piperlongumine, a natural alkaloid isolated from *Piper longum*, has attracted increasing attention due to its potent anticancer activity across multiple cancer types and, notably, its high selective pro-apoptotic activity cytotoxicity in cancer cells, a property that may help overcome the lack of selectivity associated with current pancreatic cancer therapies. In the present study, a network pharmacology approach was employed to systematically explore the molecular mechanisms underlying the anticancer potential of piperlongumine in pancreatic cancer, an area that remains insufficiently investigated.

METHOD



RESULTS & DISCUSSION

1. Intersecting genes

A total of 237 intersecting genes were identified between piperlongumine-associated targets and pancreatic cancer-related genes (Figure 1).

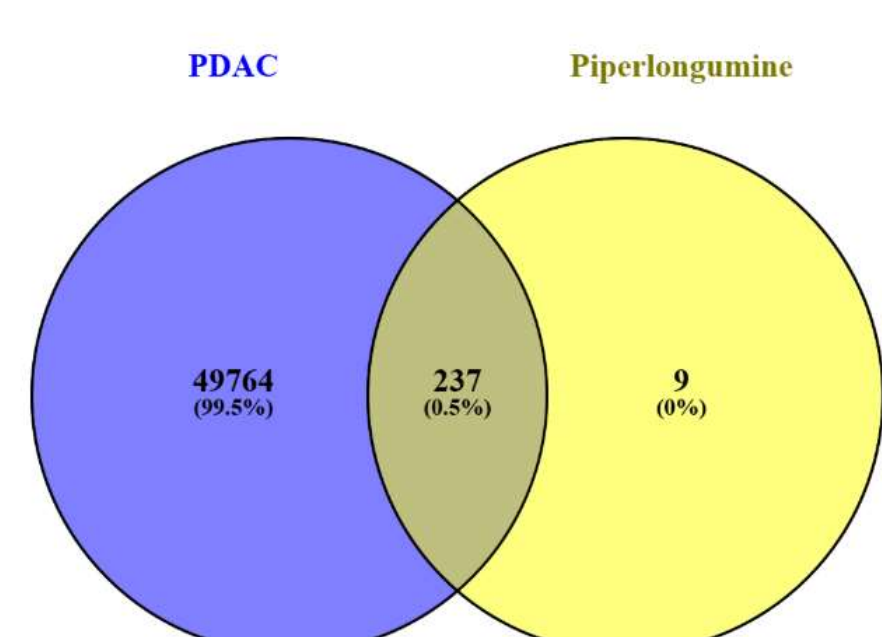


Figure 1. Venn diagram of common genes.

2. Hub genes

Network analysis revealed several central hub genes, including TP53, Akt-1, STAT-3, CTNNB-1, IL-6, TNF- α , and Bcl-2, which are critically involved in tumor progression, inflammatory signaling, and apoptosis regulation (Figure 2).

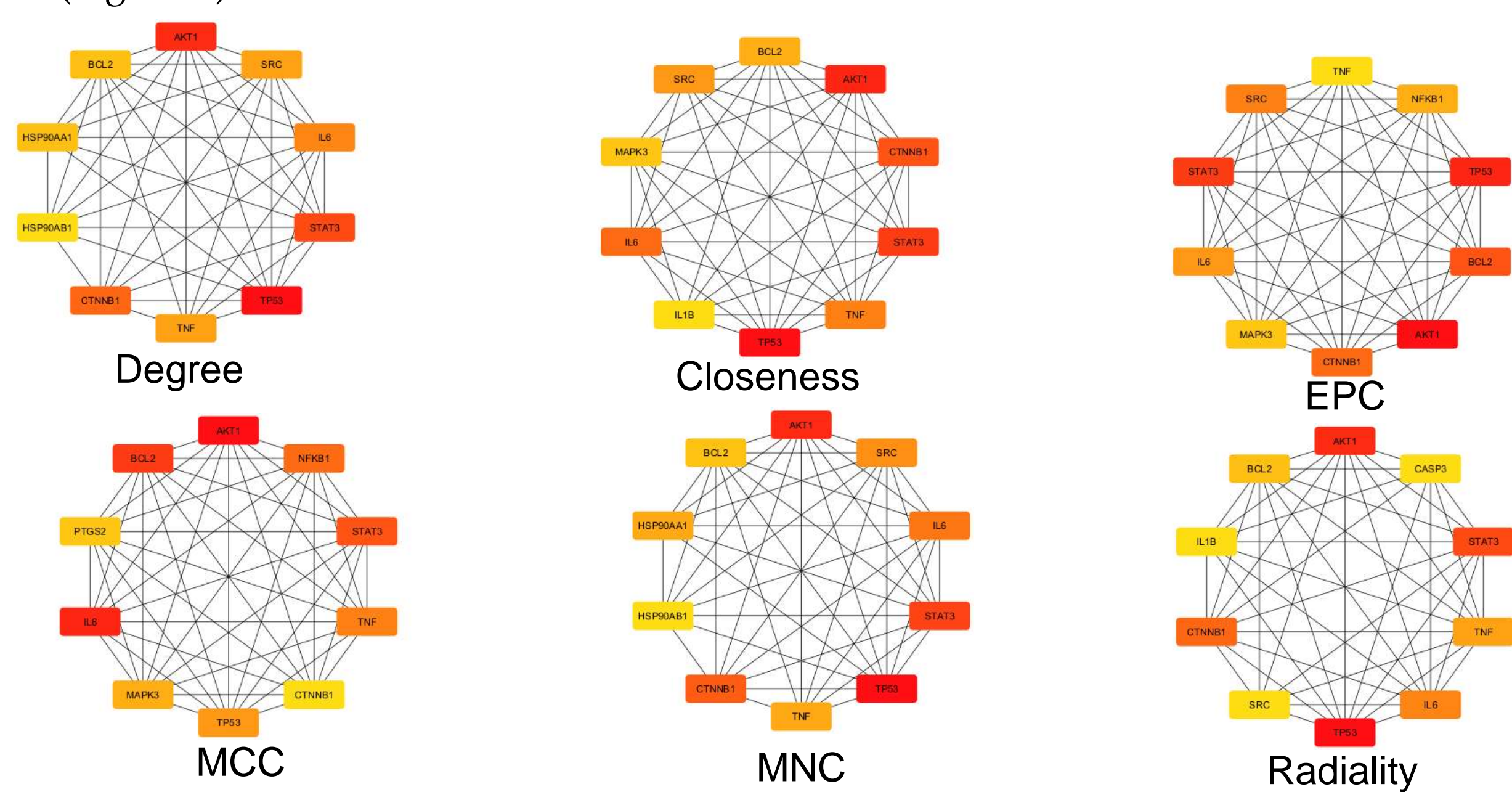


Figure 2. Topological analysis and hub genes identification.

4. Prognostic analysis of hub genes

Survival analysis revealed significant prognostic associations for several hub genes (Figure 5).

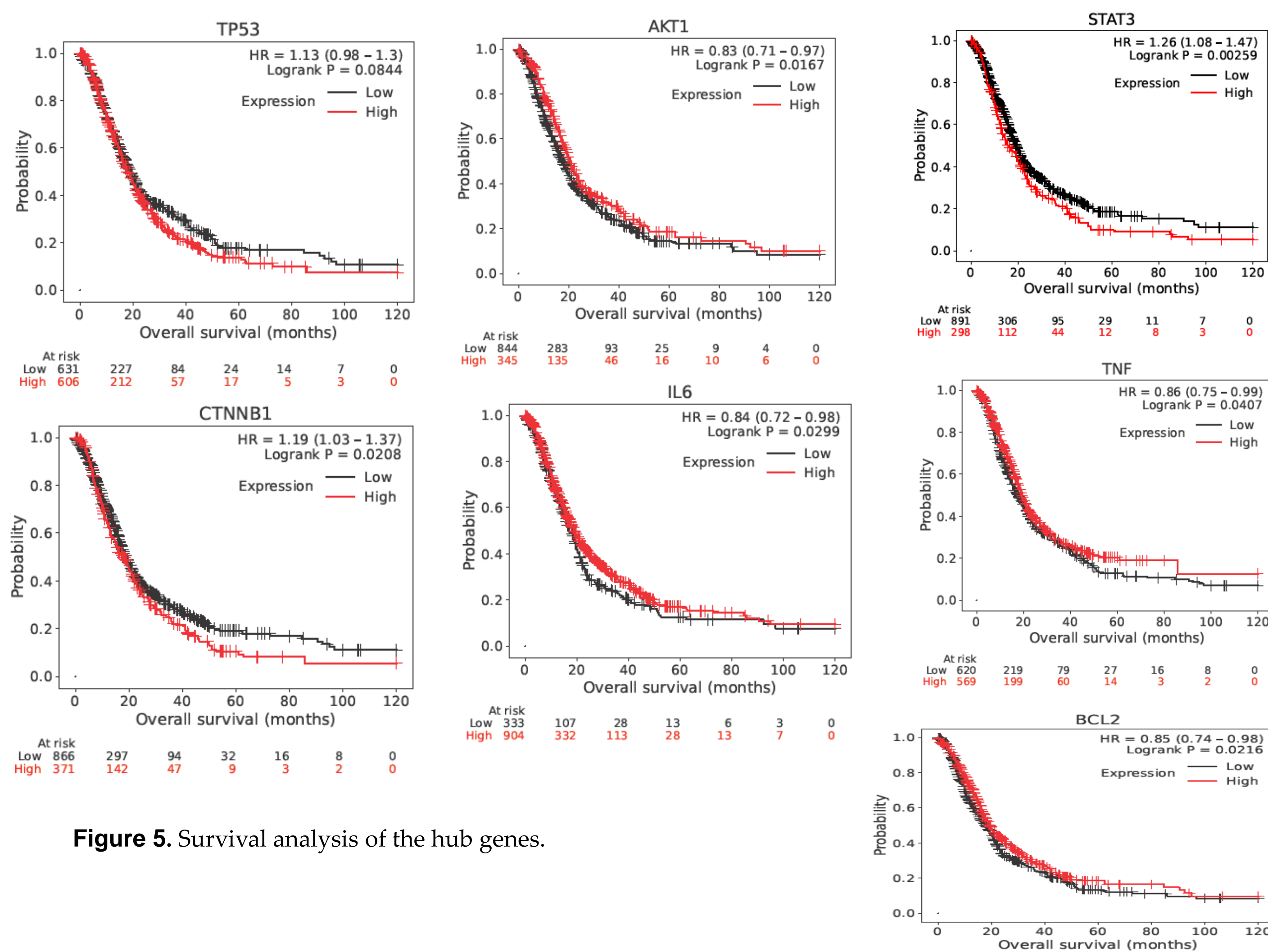


Figure 5. Survival analysis of the hub genes.

RESULTS & DISCUSSION

3. Enrichment analysis

3.1. KEGG pathway

KEGG pathway analysis highlighted pancreatic cancer as the most significantly enriched pathway (fold enrichment = 33.98; 27 genes), together with the FoxO signaling pathway, PD-1/PD-L1 immune checkpoint pathway, TNF signaling pathway, and other cancer-associated signaling pathways (Figure 3).

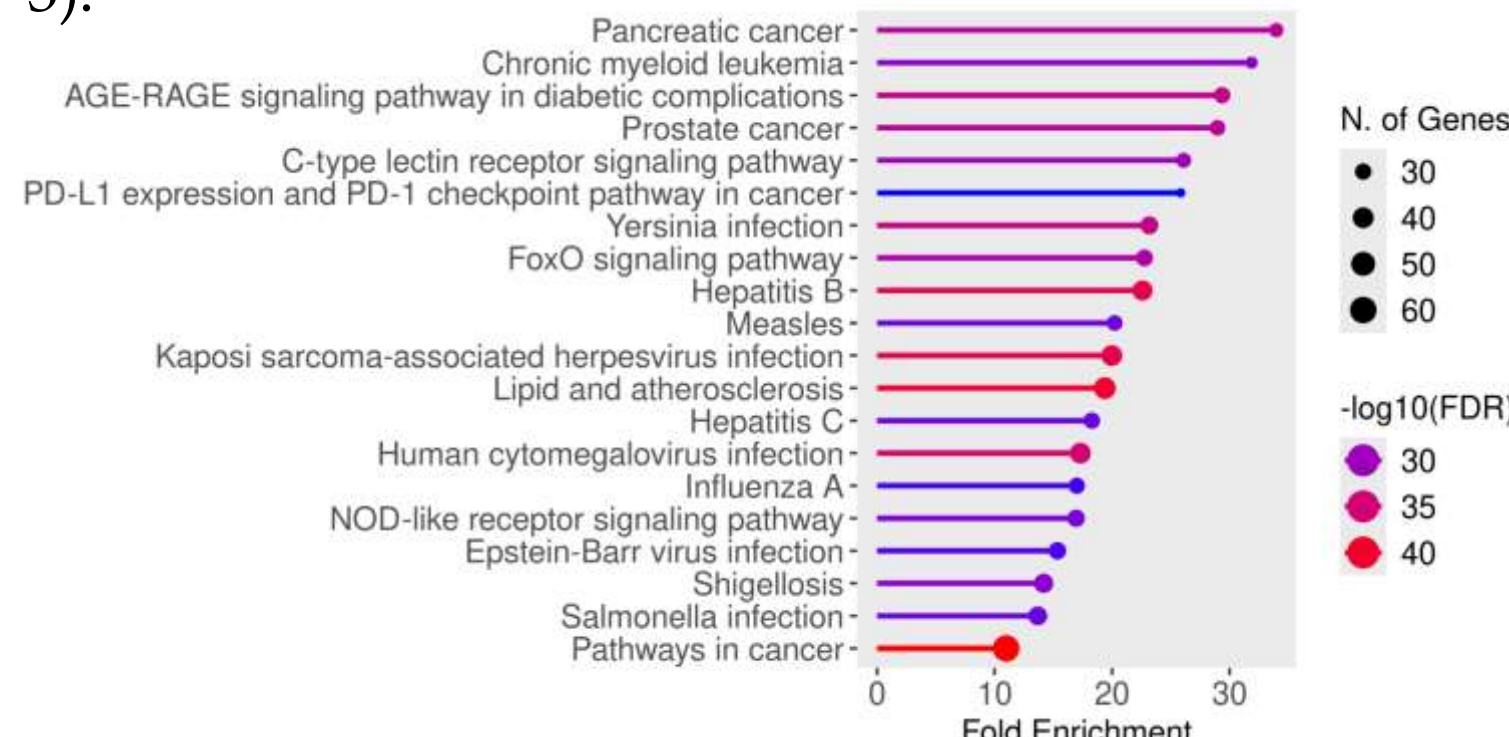


Figure 3. KEGG analysis, top 20 pathways.

3.1. Gene ontology (GO) enrichment analysis

Enrichment analysis demonstrated significant associations with biological processes such as regulation of programmed cell death, protein phosphorylation, and intracellular signal transduction (Figure 4).

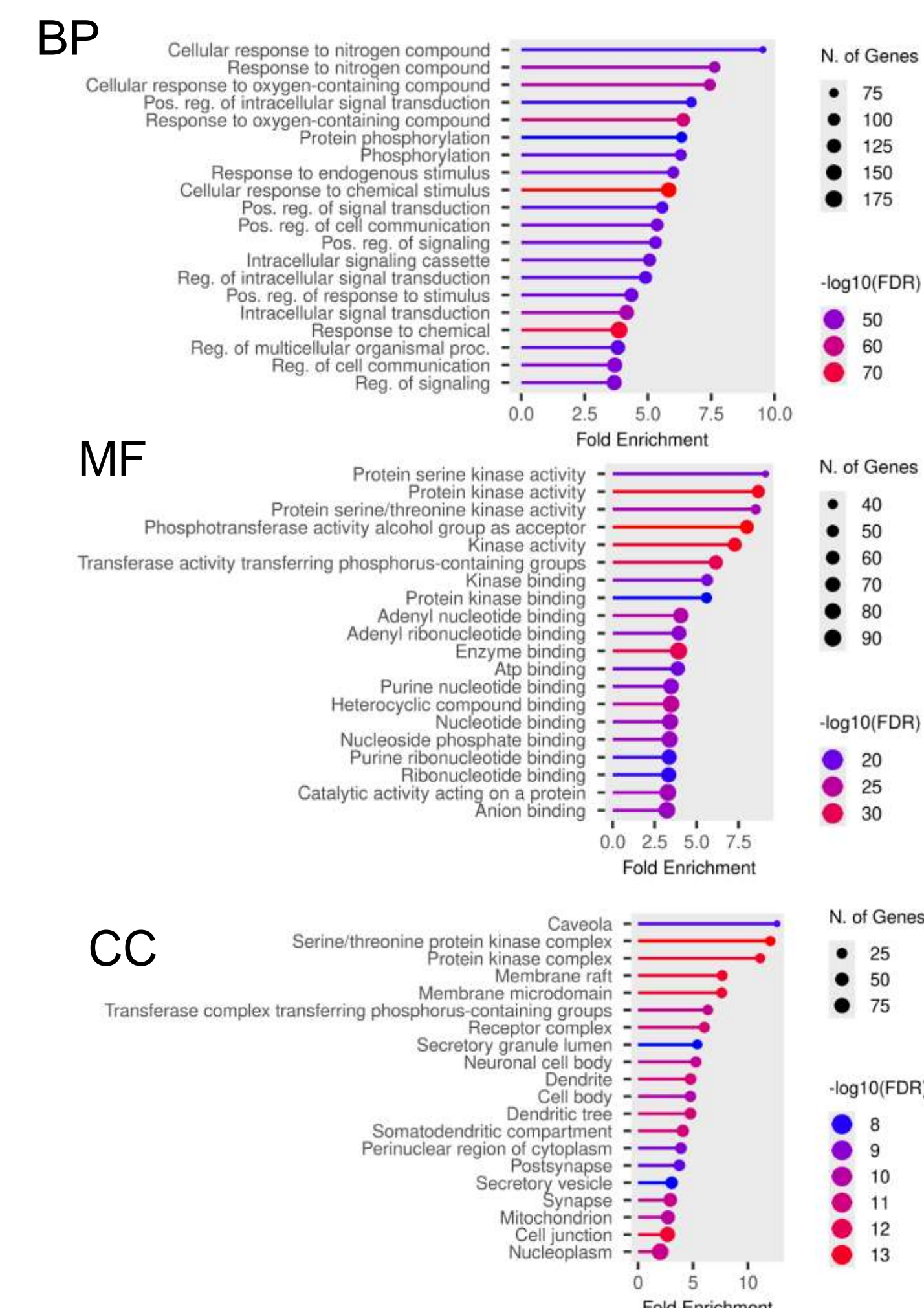


Figure 4. GO enrichment analysis, top 20 BP, MF, and CC categories.

5. Molecular docking validation

Molecular docking revealed that piperlongumine exhibited favorable binding affinities toward most targets. Particularly it showed the highest affinity toward Bcl-2 (-7.2 kcal/mol), followed by TP53 (-6.2 kcal/mol), CTNNB-1 (-6.2 kcal/mol), and Akt-1 (-5.8 kcal/mol) (Table 1).

Table 1. docking scores of piperlongumine against hub proteins.

| Target protein | Docking score (kcal/mol) |
|----------------|--------------------------|
| TP53 | -6,2 |
| AKT1 | -5,8 |
| STAT3 | -5,2 |
| CTNNB1 | -6,2 |
| IL6 | -0,38 |
| TNF | -5,2 |
| BCL2 | -7,2 |

CONCLUSIONS

Collectively, this integrative network pharmacology analysis provides novel mechanistic insights into the multi-target anticancer potential of piperlongumine in pancreatic cancer. The findings suggest that its therapeutic effects may arise from the coordinated modulation of apoptosis-related pathways, inflammatory signaling, and immune-associated mechanisms, supporting piperlongumine as a promising candidate for further experimental and translational investigations.