

Computational Drug Repurposing of H1-Antihistamines for Inhibiting Tumour Progression in Pancreatic Cancer: An In Silico Evaluation

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Abstract:

Background: Pancreatic adenocarcinoma (PAAD) is one of the most aggressive malignancies, characterized by poor prognosis, early metastasis, and limited therapeutic options. Drug repurposing has emerged as an attractive strategy for identifying novel anticancer agents by utilizing the established safety profiles of approved drugs. In this study, FDA-approved H1-antihistamines were evaluated as potential therapeutic candidates against PAAD using an integrated computational approach.

Methods: Differentially expressed genes (DEGs) associated with PAAD were identified from publicly available transcriptomic datasets obtained from TCGA and GEO. Functional enrichment, protein–protein interaction (PPI) network construction, and hub gene analysis were performed to identify key molecular targets. Selected FDA-approved H1-antihistamines were screened against hub proteins (ACTB, ITGB1, CDC42, CDK1, and CTNNB1) using molecular docking. The top-ranked compounds were further evaluated for drug-likeness, pharmacokinetic properties, and toxicity using SwissADME, Molinspiration, OSIRIS, and pkCSM.

Results: Bioinformatics analysis identified 2,000 significant DEGs and five major hub proteins involved in cell cycle regulation, cytoskeletal organization, and tumour progression. Molecular docking demonstrated that Rupatadine, Mizolastine, and Ebastine exhibited the strongest binding affinities toward the selected targets, with Ebastine showing the highest affinity for CDK1 (−10.1 kcal/mol). ADME analysis indicated favourable oral bioavailability and acceptable drug-likeness, while toxicity predictions suggested that Rupatadine possessed the most balanced safety profile.

Conclusion: The findings suggest that second-generation H1-antihistamines, particularly Rupatadine, represent promising candidates for repurposing as potential therapeutics for pancreatic adenocarcinoma. Further in vitro and in vivo studies are required to validate these computational predictions and assess their clinical applicability.

Keywords: Pancreatic adenocarcinoma; Drug repurposing; H1-antihistamines; Molecular docking; Bioinformatics.

1. Introduction

Pancreatic adenocarcinoma (PAAD) is among the most aggressive human malignancies. It continues to pose a major challenge to global healthcare because of its rapid progression, limited therapeutic responsiveness, and poor long-term survival. Despite substantial advances in cancer biology, precision medicine, and targeted therapeutics, the prognosis of patients diagnosed with pancreatic adenocarcinoma remains dismal. The disease is characterised by extensive

molecular heterogeneity, early metastatic dissemination, and a highly immunosuppressive tumour microenvironment, which collectively contribute to therapeutic resistance and disease recurrence. Consequently, pancreatic adenocarcinoma remains one of the leading causes of cancer-related mortality worldwide and represents an urgent unmet medical need ^[1].

PAAD develops because of changes in the genes and other regulatory mechanisms that control how cells grow, divide, and die. These changes allow cancer cells to multiply quickly, avoid natural cell death, spread to nearby tissues and distant organs, and form new blood vessels that supply nutrients to the tumour. Several important cell communication pathways, such as KRAS, PI3K/AKT, MAPK/ERK, TGF- β , Wnt/ β -catenin, and JAK/STAT, become overactive and help the cancer grow and resist treatment. At the same time, the loss of protective genes like TP53, CDKN2A, and SMAD4 removes the normal controls that prevent abnormal cell growth. Understanding these molecular changes helps researchers identify new targets for drug discovery and develop better treatments using computational methods ^[2].

Recent advances in high-throughput sequencing technologies and public cancer databases have significantly improved the understanding of pancreatic adenocarcinoma biology. Integrative analyses using resources such as The Cancer Genome Atlas (TCGA), Gene Expression Omnibus (GEO), and other transcriptomic repositories have enabled the identification of differentially expressed genes, prognostic biomarkers, and dysregulated signalling networks associated with tumour progression. Bioinformatics analyses further facilitate the discovery of hub genes, protein–protein interaction networks, immune infiltration patterns, and potential therapeutic targets that can accelerate drug discovery while reducing experimental costs ^[3].

Among the numerous molecular regulators implicated in pancreatic adenocarcinoma, G protein-coupled receptors (GPCRs) have emerged as attractive therapeutic targets because they regulate diverse biological processes, including proliferation, migration, inflammation, angiogenesis, and immune modulation. GPCRs represent one of the largest families of membrane receptors and constitute targets for approximately one-third of currently approved drugs. Several GPCRs are aberrantly expressed in pancreatic adenocarcinoma, suggesting that pharmacological modulation of these receptors may provide novel therapeutic opportunities through drug repurposing strategies ^[4].

Drug repurposing is a faster and more affordable way to discover new cancer treatments by using medicines that are already approved for other diseases. Since these drugs have established safety profiles, they can be developed more quickly than new drugs ^[2]. Studies suggest that some second-generation H1-antihistamines, including loratadine, desloratadine, and ebastine, may have anticancer effects. These medicines are considered good candidates for repurposing because they are safe and have well-known pharmacological properties. Computer-based methods help researchers predict how these drugs interact with cancer-related targets before laboratory testing. This approach reduces both the time and cost required to identify promising treatments for pancreatic adenocarcinoma ^[5].

Mechanism of H1-antihistamines in Cancer

Histamine is a naturally occurring molecule produced from the amino acid histidine by the enzyme histidine decarboxylase (HDC). It acts through four receptors (H1R–H4R) to regulate various biological functions. In addition

to its role in allergies and inflammation, histamine also contributes to cancer development by promoting tumour growth, blood vessel formation, and the spread of cancer cells [6]. Among its receptors, the histamine H1 receptor (HRH1) plays an important role by activating signalling pathways that support cancer cell survival, proliferation, and metastasis. Therefore, blocking HRH1 has emerged as a promising strategy for cancer treatment [7].

H1-antihistamines are commonly used to treat allergic diseases, but they have recently gained attention as potential anticancer drugs through drug repurposing. These drugs block the histamine H1 receptor (HRH1), reducing signalling pathways that promote cancer cell growth, survival, migration, and angiogenesis. Some H1-antihistamines, such as loratadine, desloratadine, diphenhydramine, and cetirizine, can also induce cancer cell death through additional mechanisms independent of HRH1 [8]. They may also improve the tumour microenvironment by reducing immune suppression and enhancing the body's antitumour immune response. Furthermore, H1-antihistamines can increase the effectiveness of chemotherapy and help overcome drug resistance. Their established safety profile and multiple anticancer mechanisms make them promising candidates for cancer treatment [5].

Therefore, this study uses computer-based methods to evaluate approved H1-antihistamines as potential treatments for pancreatic adenocarcinoma. Bioinformatics, molecular docking, and pharmacokinetic analyses were performed to study how these drugs interact with important cancer-related targets. The aim is to identify promising drugs that could be repurposed for the treatment of pancreatic adenocarcinoma.

2. Materials and Methods

2.1 Data Collection and DEG Analysis

The data used for splicing analysis were downloaded from The Cancer Genome Atlas (TCGA) SpliceSeq database (<https://bioinformatics.mdanderson.org/TCGASpliceSeq/singlegene.jsp>) on 3rd January 2022, and per cent spliced in (PSI) values of 0 or 1 were filtered out. The TCGA-PAAD expression and mutation profile data were downloaded from Xena [9] (Table 1). In addition, clinical and follow-up information were acquired from the same database. The bulk transcriptome dataset and single-cell dataset were downloaded from the Gene Expression Omnibus (GEO) database [10]. We performed pretreatment for gene chip data as follows:

- (I) The probe was mapped to the gene according to the annotation file;
- (II) The empty probe was removed, and
- (III) The maximum value corresponding to the same gene was selected as the expression level of the gene.

Table 1. Public datasets used in this study

Database	Data Type	Samples	Purpose
TCGA SpliceSeq	Alternative splicing (PSI values)	178	Alternative splicing analysis

UCSC Xena	RNA-seq expression	178 tumour, 4 normal	Differential gene expression
UCSC Xena	Clinical data	178	Survival and clinicopathological analysis
UCSC Xena	Somatic mutation data	178	Mutation analysis

Data Acquisition: Transcriptomic data for pancreatic adenocarcinoma (PAAD) were retrieved from the Genotype-Tissue Expression (GTEx) and The Cancer Genome Atlas (TCGA) databases via the GEPIA2 platform ^[11]. GEPIA2 integrates RNA sequencing expression data from TCGA and GTEx, providing a comprehensive resource for gene expression profiling and interactive analyses.

Differential Expression Analysis: Differentially expressed genes (DEGs) between PAAD tumor tissues and normal pancreatic tissues were identified using GEPIA2's differential expression analysis module ^{[12], [13]}. The criteria for DEG selection were set as $|\log_2 \text{fold change}| \geq 1$ and adjusted p-value (q-value) < 0.01 . These thresholds ensure the identification of genes with statistically significant and biologically relevant expression changes ^[14].

2.2 Functional Enrichment Analysis

Analysis and identification of hub genes. Hub genes were excavated with a cut-off value for degrees ≥ 10 . Subsequently, Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) analyses were used to functionally annotate the hub genes ^[15].

Gene Ontology (GO) and Pathway Enrichment: To elucidate the biological significance of the differentially expressed genes (DEGs) identified in pancreatic adenocarcinoma (PAAD), functional enrichment analyses were performed. The DEGs were input into the Enrichr platform ^[16], which facilitates comprehensive enrichment analyses across various biological databases.

- **Gene Ontology (GO) Biological Process (BP) Analysis:** The DEGs were analyzed for enrichment in processes and biological objectives to which the genes contribute.
- **Pathway Analysis by Kyoto Encyclopedia of Genes and Genomes (KEGG):** To identify metabolic and signalling pathways associated with the DEGs.
- Enrichment results were considered statistically significant based on adjusted p-values (q-values) < 0.05 . The top enriched GO terms and pathways were visualized using bar plots to facilitate interpretation.

2.3 Protein-Protein Interaction (PPI) Network

Network Assembly: To investigate the interactions among the DEGs, a PPI network was constructed using the STRING database ^[17]. STRING integrates known and predicted protein-protein associations derived from various

sources, including experimental data, computational prediction methods, and public text collections. The interaction score threshold was set to high confidence (≥ 0.7)

Visualization and Analysis: The resulting PPI network was imported into Cytoscape (version 3.9.1) for visualization and further analysis. Within Cytoscape, topological analyses such as degree centrality and betweenness centrality were performed to identify hub proteins with the highest number of connections and determine the proteins that act as bridges within the network, respectively.

Construction of the protein–protein interaction (PPI) network and identification of significant modules Search Tool for the Retrieval of Interacting Genes (STRING) was used to construct the DEG PPI network. A confidence score > 0.7 was set as the criterion of judgment. Next, the most significant modules of the network map were identified using Molecular Complex Detection (MCODE) (version 1.5.1, Cytoscape plug-in) using the default parameters

2.4 Ligand Selection and Preparation

A selection of FDA-approved second-generation H1-antihistamines was made based on their established pharmacological profiles and potential anticancer properties. These compounds were chosen due to their known safety in humans and emerging evidence suggesting their efficacy in oncology settings. Structure of H1-antihistamine shown in Figure 1

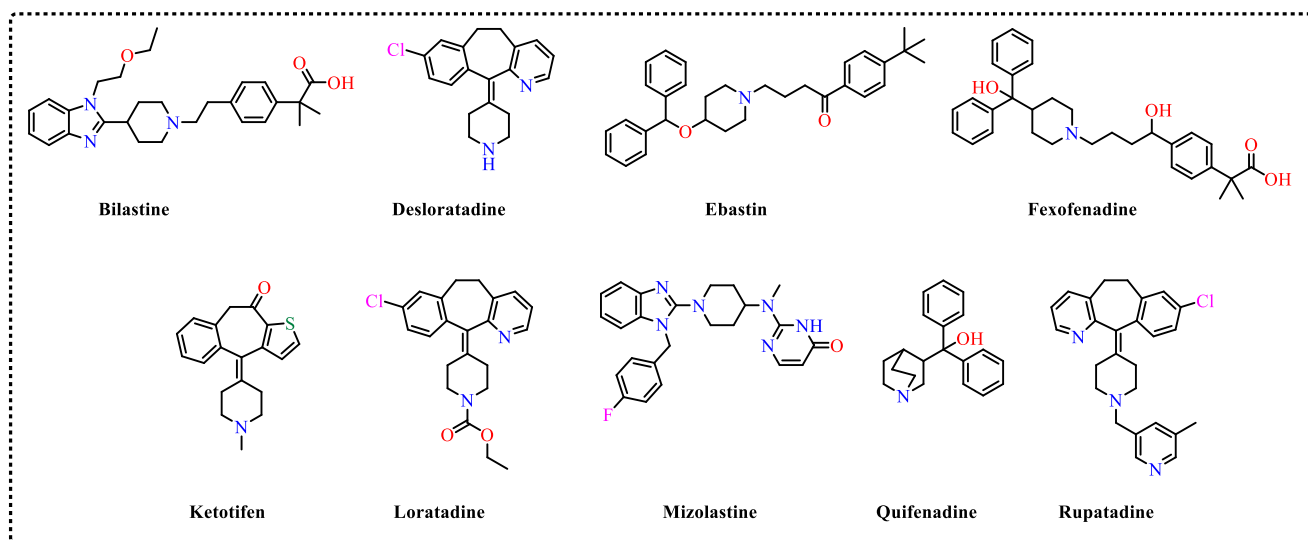


Figure 1: Chemical structures of FDA-approved H1-antihistamine drugs.

The three-dimensional structures of the selected ligands were obtained from the PubChem database^[18] in “sdf” format. Convert the “sdf” file into “pdb” format. And minimise energy for respective structures. The prepared structures were saved in PDBQT format, compatible with the docking software.

2.5 Molecular Docking

Virtual screening is a computational technique used in drug discovery to search libraries of small molecules in order to identify those structures that are most likely to bind to a drug target, typically a protein receptor or enzyme. It is an important tool in the discovery of novel drugs, representing a cost-effective and efficient method to screen lakhs of

compounds for target-specific binding. Virtual screening was done by AutoDock version 4 using the PyRx interface. Crystal structures of the target proteins were downloaded from PDB ^[19] in .pdb format. Protein IDs for each hub gene are **shown in table-2**. Each structure was uploaded in PyRx as a macromolecule and converted to pdbqt format. The library of FDA-approved drugs was downloaded from the PubChem database as in .sdf format. This was also converted to .pdbqt format and uploaded as ligands in PyRx. A grid was designed in PyRx as “Vina Search Space” around the active site of the protein, which was identified through PDBsum as the active amino acid residues involved in protein-protein/ protein-ligand interactions. The exhaustiveness in search parameters in the Vina wizard was set to 8, so that each compound could be modelled into the target site with different conformations. Virtual screening was then executed between the protein and the compounds library (both in .pdbqt formats) in the defined search space. Scores in the form of binding energies between the compound and the active site of the protein were obtained. The lower the binding energy, the higher the affinity of the compound for the target site of the protein. The protein-ligand complexes were visualised using Biovia. Drug targets were analysed based on their Vina scores

Table 2: Protein IDs

Hub Gene	Protein Id	Resolution (Å)
ACTB	1J6Z	2.00
ITGB1	3VI3	2.90
CDC42	1A42	1.70
CDK1	4YC6	2.70
CTNNB1	1JDH	2.50

2.6 Pharmacokinetic Analysis

The pharmacokinetic profiles of the selected H1-antihistamines (mizolastine, rupatadine, and ebastine) were evaluated using the SwissADME web tool ^[20]. The Lipinski parameters, topological polar surface area (TPSA), molar volume (MV) and rotatable bonds (RB) were calculated using Molinspiration, a free web JME editor. According to the rule of five (RO5), the molecules show good oral absorption when the values of MW are less than 500, calculated Log P (cLog P) is less than 5, HBD and HBA are less than 5 and 10, respectively. Other parameters, such as synthetic accessibility and bioavailability score, were computed using the SwissADME online tool ^[20]. This platform provides in silico predictions of absorption, distribution, metabolism, and excretion (ADME) parameters, which are critical for assessing the drug-likeness of compounds.

2.7 Toxicity Prediction

Toxicity of the selected H1-antihistamines (mizolastine, rupatadine, and ebastine) were drugs were predicted using OSIRIS property explorer^[21] and pkCSM^[22]. OSIRIS software helps in the prediction of pharmacokinetic parameters such as cLogP, solubility, molecular weights, drug- likeness, etc and also toxicity parameters such as mutagenicity, irritancy, tumorigenicity and reproductive toxicity. Predicted results are valued and are colour-coded. Properties with high risks of undesired effects, such as mutagenicity or poor intestinal absorption, are shown in red. Whereas a green colour indicates drug-like behaviour. pkCSM software helps in prediction of LD₅₀, LOAEL, Hepatotoxicity, Skin sensitivity and T.pyriformis toxicity.

3. Results and Discussion

3.1 Identification of common differentially expressed genes (DEGs)

Gene expression datasets from GEO database were used to analyze DEGs in PAAD and PAAD versus normal samples. Of the 9,219 differentially expressed genes obtained, further studies were limited to the 2,000 most relevant genes of the obtained data. DEGs between control and PAAD, and control and PAAD populations were identified using the Network Analyst server using a random-effects model (REM). REM takes into account sampling error and differences in study characteristics, such as the experimental design, sample size, or study population, which are considered “random effects”, and which contribute to the overall variability in effect sizes across studies. It considers both within-study and between-study variability when estimating the overall effect size (ES). REM assumes that the ESs of individual studies are not identical but follow a distribution, and assigns weights to each study based on the sample size and estimated variances, which allows for a more robust and consistent conclusion regarding gene expression patterns across multiple studies. The results revealed a total of the 9,219 differentially expressed genes obtained, further studies were limited to the 2,000 most relevant genes of the obtained data. Common in all PAAD and PAAD datasets that were analyzed. Upregulated genes with > 1 combined effect size were selected for further analyses

3.2 Enrichment analysis

The enrichment analysis yielded several significantly overrepresented GO terms, primarily related to cell migration, extracellular structure, and immune processing. The top enriched terms are depicted in the bar plot (Figure 2). The genes were subjected to enrichment analysis

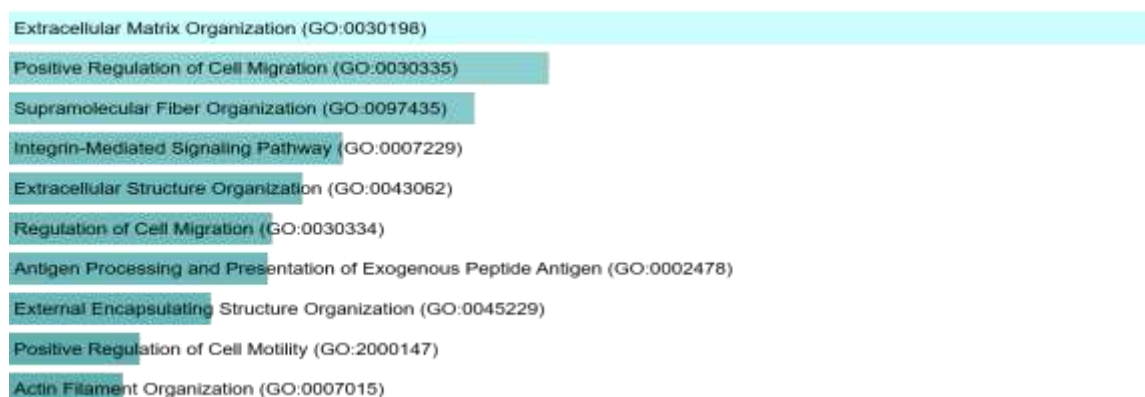


Figure 2: GO Biological Process

KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway analysis is an essential approach to map differentially expressed genes (DEGs) to known biological pathways. This helps researchers to identify systemic functions and molecular interactions associated with experimental conditions such as disease, treatment, or environmental stress. In this analysis, KEGG enrichment was used to highlight relevant biological pathways significantly impacted by the gene expression changes.

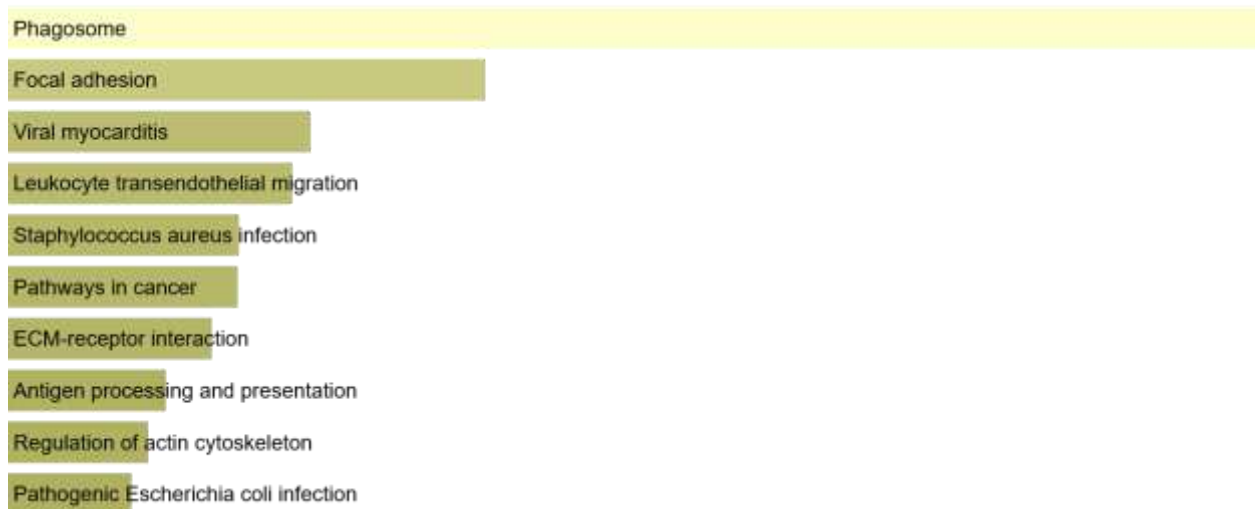


Figure 3: KEGG Pathways

Among the analyzed proteins, **ACTB** (Actin Beta) exhibits the highest degree (40), suggesting its central role in maintaining cytoskeletal integrity and facilitating interactions with multiple cellular components. **ITGB1** and **CDC42** are also prominent, indicating their involvement in cell communication and structural dynamics. **CDK1** and **CTNNB1** are critical regulators of the cell cycle and transcription, respectively.

These hub proteins are potential candidates for further study as they may serve as biomarkers or therapeutic targets in disease-related pathways.

Table 3: PPI Network Analysis

Protein	Degree	Function
ACTB	40	Actin polymerizes to produce filaments that form cross-linked networks in the cytoplasm of cells.
ITGB1	34	Integrin beta 1 plays a crucial role in cell adhesion and signalling
CDC42	32	Cell division control protein 42

CDK1	30	Cyclin-dependent kinase 1 promotes G2-M transition, and regulates G1 progress and G1-S transition
CTNNB1	29	CTNNB1 acts as a coactivator for transcription factors

Protein-Protein Interaction (PPI) networks were constructed to explore the functional connectivity among key proteins involved in the biological system under study. The first network (Figure 5) reveals a dense, modular architecture that highlights multiple hubs, including ACTB, ITGB1, CDK1, and CDC42, which are associated with cytoskeletal organisation, signal transduction, and cell cycle regulation.

The second image (Figure 6) presents a broader interaction landscape involving several hundred proteins, indicating a complex web of interactions. Central clusters represent core biological processes, while peripheral nodes likely reflect specialized functions.

Color-coded edges in both networks signify different interaction types, such as co-expression, experimental validation, or database-derived predictions. The dense core implies functional centrality, with hub proteins likely acting as regulatory or structural scaffolds.

This comprehensive interaction mapping underscores the biological significance of high-degree proteins and provides insight into potential therapeutic or diagnostic targets. The PPI analysis supports further in silico and wet-lab validation of these central proteins in disease mechanisms.

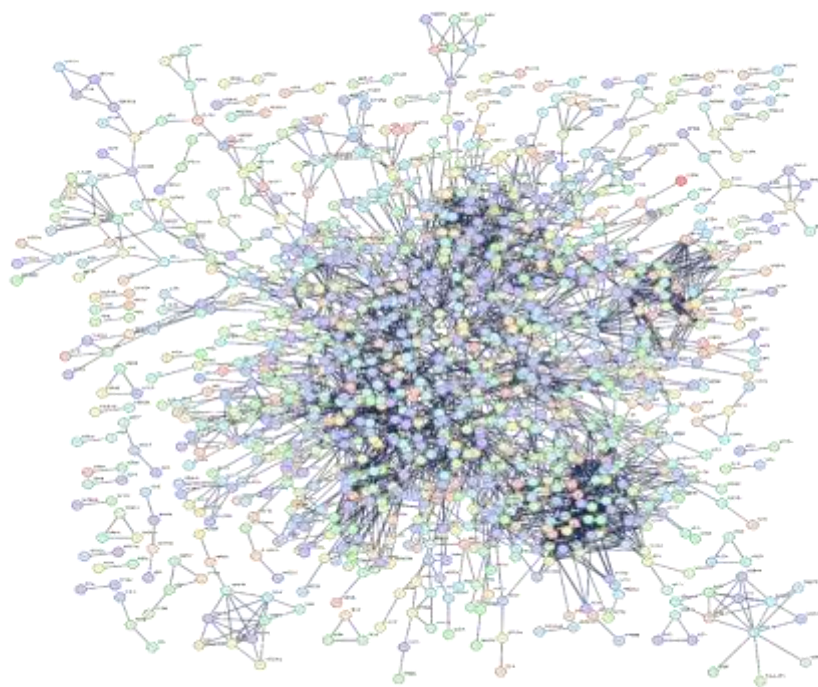


Figure 4: PPI Network Analysis

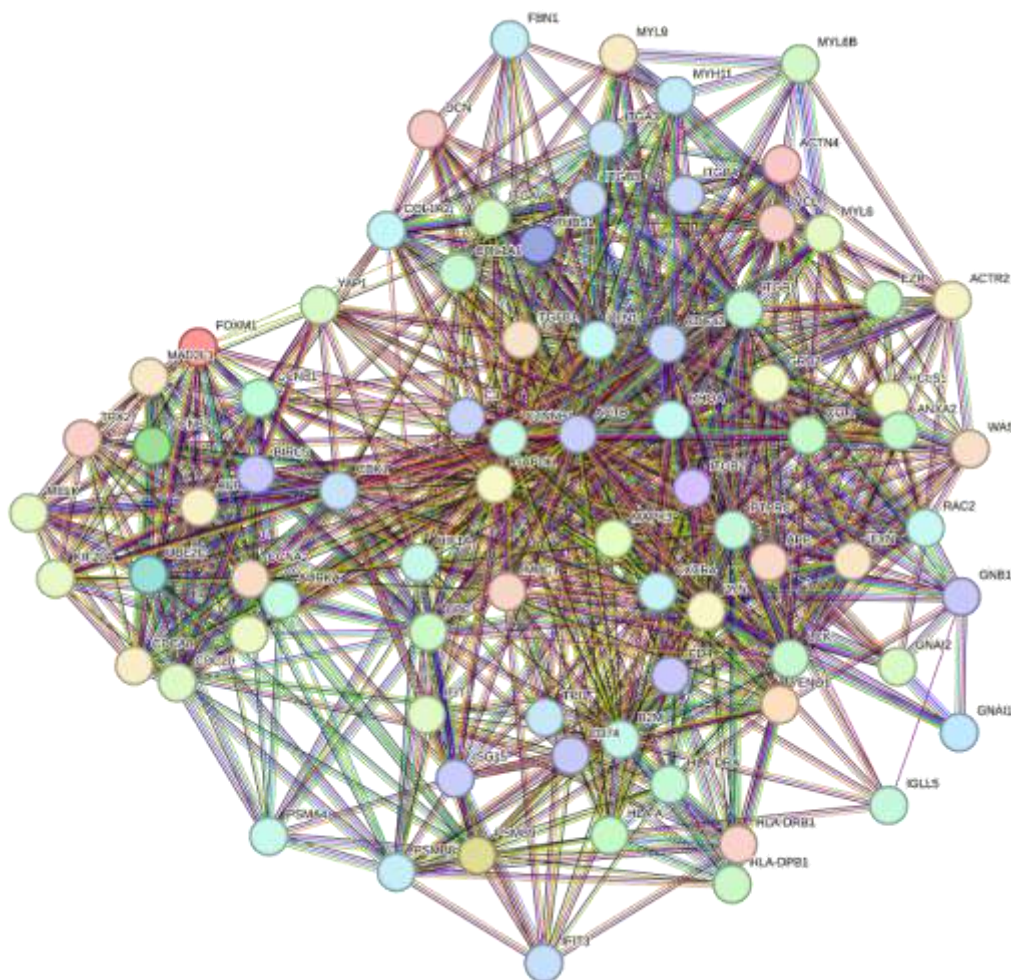


Figure 5: PPI Network Analysis

3.3 *In silico* Docking studies

Molecular docking was performed to evaluate the binding affinities of selected antihistamines with key proteins (CDC42, CDK1, CTNNB1, ITGB1, and ACTB) involved in cellular regulation and signal transduction. Among the compounds tested, Ebastin, Mizolastine, and Rupatadine consistently demonstrated strong binding affinities across all targets, with Ebastin showing the highest affinity towards CDK1 (-10.1 kcal/mol) and ITGB1 (-10 kcal/mol).

Mizolastine showed notable binding with ACTB (-9.7 kcal/mol) and CDK1 (-9.4 kcal/mol), while Rupatadine had high affinity for all proteins, especially ACTB (-9.9 kcal/mol) and CDK1 (-9.5 kcal/mol). Other compounds like Desloratadine and Fexofenadine also exhibited significant interactions, particularly with CDK1 and ITGB1. Docking results shown in Table 4.

Table 4: Docking results

Drug Compound/Protein	CDC42	CDK1	CTNNB1	ITGB1	ACTB
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Bilastine	-8.2	-8.8	-7.8	-8.2	-9.1
Desloratadine	-8.5	-9.3	-8.6	-8.7	-8.2
Ebastin	-9.0	-10.1	-8.7	-10	-9.6
Fexofenadine	-8.5	-10	-8.5	-9.6	-9.0
Ketotifen	-7.9	-8	-8.5	-9.0	-7.8
Loratadine	-8.2	-7.3	-8.5	-9.4	-8.7
Mizolastine	-8.8	-9.4	-8.8	-9.8	-9.7
Quifenadine	-7.9	-9	-7.3	-8.8	-7.9
Rupatadine	-9.2	-9.5	-9.3	-9.3	-9.9

3.4 Molecular Docking Visualization Report

The image above illustrates the docking poses of selected H1-antihistamines (in blue) within the active sites of five key target proteins (in green ribbon structure), including CDC42, CDK1, ITGB1, ACTB, and CTNNB1, identified as hub proteins in the PAAD protein interaction network. Each protein-ligand complex was visualized in 3D to confirm the binding conformation and proper accommodation of the ligand within the active site. The ligands exhibit close interaction with the core catalytic or binding residues, indicating a strong and specific fit. The spatial orientation of the ligands within the binding pocket supports the docking score results, where compounds such as Ebastine, Rupatadine, and Mizolastine showed high binding affinities (ranging from -9.4 to -10.1 kcal/mol). These visualizations confirm the structural compatibility between the antihistamines and the active regions of the hub proteins. This structural validation strengthens the hypothesis that these drugs may effectively inhibit or modulate the function of key PAAD-related proteins.

Overall, the docking images provide qualitative support for the quantitative docking scores and enhance the understanding of potential binding mechanisms, which is essential for guiding future structure-based drug design or *in vitro* validation. Docking images are shown in Figure 6.

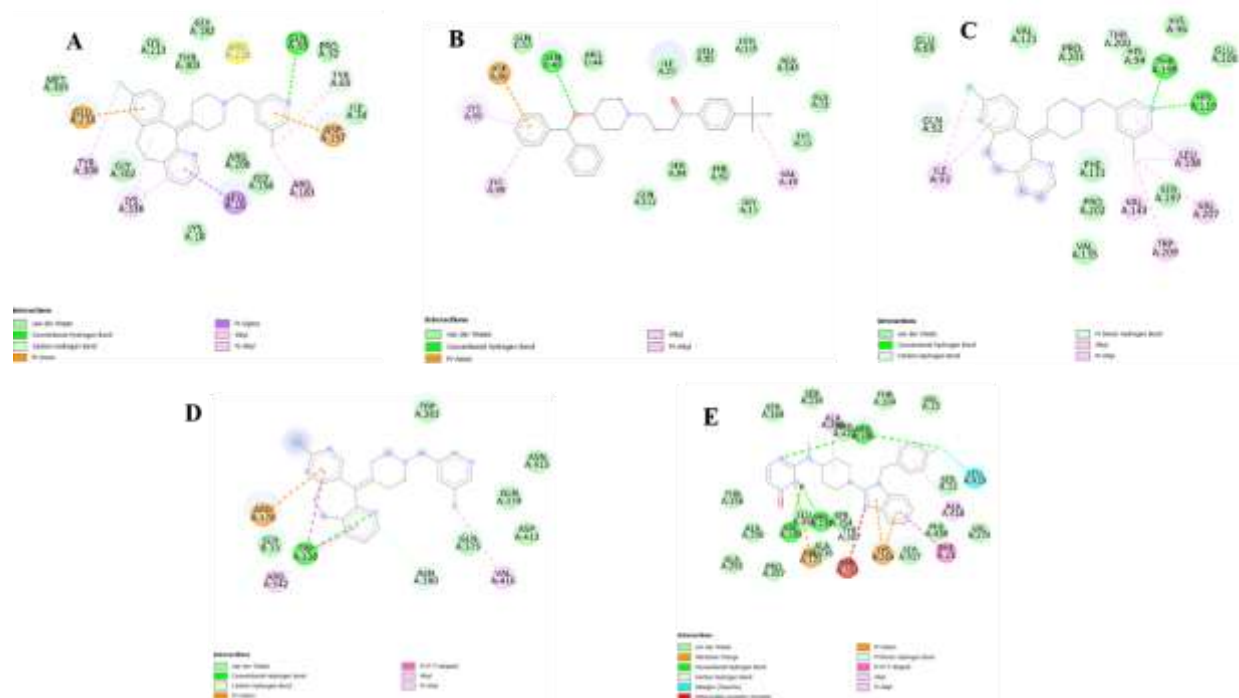


Figure 6: Docking images, A) ACTB Rupatadine, B) CDK1 Ebastine, C) CDC42 Rupatadine, D) TNNB1 Rupatadine, E) ITGB1 Mizolastine

3.5 Drug-likeness evaluation:

The pharmacokinetic evaluation of Mizolastine, Rupatadine, and Ebastine was conducted based on key ADME parameters and drug-likeness filters. All three compounds exhibited high gastrointestinal (GI) absorption, indicating good oral bioavailability. Additionally, they were identified as P-glycoprotein (P-gp) substrates, which may influence their efflux and cellular retention. Mizolastine and Rupatadine showed favorable blood-brain barrier (BBB) permeability, suggesting potential central nervous system (CNS) activity, whereas Ebastine lacked BBB permeability, limiting its CNS effects. In terms of Lipinski's Rule of Five, Mizolastine and Rupatadine showed zero violations, indicating strong drug-likeness, while Ebastine had one violation, primarily due to its higher LogP (6.17) value, indicating increased lipophilicity.

Topological Polar Surface Area (TPSA) and hydrogen bonding profiles further revealed that Mizolastine had the highest polar surface area (70.05 Å²), which may support better solubility and membrane transport. Ebastine, despite having 10 rotatable bonds, maintained a bioavailability score of 0.55, similar to the other two compounds. In conclusion, all three molecules exhibit favorable oral bioavailability, with Mizolastine and Rupatadine showing better drug-likeness due to optimal molecular properties and compliance with Lipinski's criteria. Drug likeness results are shown in Table 5.

Table 5: Drug likeness results

Parameter	Mizolastine	Rupatadine	Ebastine
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Molecular Weight	432.49 g/mol	415.96 g/mol	469.66 g/mol
LogP	3.28	5.06	6.17
Topological Polar Surface Area	70.05 Å ²	29.02 Å ²	29.54 Å ²
H-bond Donors / Acceptors	5	3	3
Rotatable Bonds	5	2	10
GI Absorption	High	High	High
P-gp Substrate	Yes	Yes	Yes
BBB Permeability	Yes	Yes	No
Lipinski Rule Violations	0	0	1
Bioavailability Score	0.55	0.55	0.55

3.6 Toxicity Studies

The toxicity prediction of Mizolastine, Rupatadine, and Ebastine was evaluated based on LD₅₀ values, organ-specific toxicity, immunotoxicity, and potential interactions with cytochrome P450 (CYP) enzymes.

LD₅₀ values (oral, rat) indicate the acute toxicity ranking as follows: Ebastine (4000 mg/kg) > Rupatadine (1000 mg/kg) > Mizolastine (450 mg/kg), suggesting that Ebastine is the least acutely toxic, while Mizolastine shows the highest acute toxicity.

Hepatotoxicity probabilities were highest for Ebastine (0.98), indicating a greater risk of liver-related adverse effects. In contrast, Mizolastine (0.68) and Rupatadine (0.80) showed moderate hepatotoxic potential.

Immunotoxicity scores revealed that Mizolastine (0.96) may cause the most immune-related side effects, followed by Ebastine (0.71) and Rupatadine (0.61), which suggests Rupatadine has the most favorable immunological safety profile.

Carcinogenicity predictions were moderate across all three, with Rupatadine (0.78) indicating the highest potential, while Ebastine (0.5) had the lowest.

Cytochrome P450 interaction analysis showed high likelihoods of interaction with CYP1A2 and CYP2C19 for all three compounds, particularly Ebastine, which had the highest scores (CYP1A2: 0.95, CYP2C19: 0.87), suggesting potential drug–drug interaction risks via metabolic pathways.

In summary, while Ebastine shows the lowest acute toxicity, it also poses higher risks for hepatotoxicity and metabolic interactions. Rupatadine appears to be the safest overall in terms of immunotoxicity and carcinogenicity, with a balanced toxicity and metabolic profile. Toxicity results are shown in Table 6.

Parameter	Mizolastine	Rupatadine	Ebastine
LD ₅₀	450mg/kg	1000mg/kg	4000mg/kg
Hepatotoxicity	0.68	0.8	0.98
Immunotoxicity	0.96	0.61	0.71
Carcinogenicity	0.6	0.78	0.5
CYP1A2	0.86	0.74	0.95
CYP2C19	0.71	0.61	0.87

Table 6: Toxicity results

4. Discussion

Of the 2000 DEGs, the main hub genes were determined to be ACTB, CDC42, CDK1, ITGB1, CTNNB. Rupatadine shows the greatest promise against PAAD DEGs, with Mizolastine following. Although Ebastine faces various pharmacokinetic challenges, its pharmacological activity is remarkable and so various formulation aspects may negate the pharmacokinetic shortcomings. Further *in vivo* studies are essential to confirm these findings. This study highlights the potential of repurposing H1-antihistamines for PAAD treatment. Several compounds showed strong binding affinity, favorable ADME properties, and low predicted toxicity. These findings require further validation through laboratory and clinical studies to explore their real-world therapeutic viability.

5. Conclusion

This research the potential of repurposing second-generation H1-antihistamines as therapeutic agents for pancreatic adenocarcinoma. Rupatadine emerged as the most promising candidate based on its favorable pharmacokinetic profile, strong binding affinities, and balanced toxicity profile. Mizolastine and Ebastine also showed significant anticancer potential but with varying limitations related to toxicity and drug-likeness. These findings offer a valuable foundation for further *in vitro* and *in vivo* validation studies. If confirmed, these agents could represent an innovative and cost-effective approach to improving treatment outcomes in PAAD.

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