BIO Web of Conferences **233**, 01015 (2026) https://doi.org/10.1051/bioconf/202623301015
ICABB 2026

Integrated Bioinformatics and Experimental Validation of Shared Genetic Targets in AKI and Ovarian Cancer for reserpine-based Therapeutics

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Abstract

Introduction: Ovarian cancer (OC) is the most lethal and common malignancy among women. Patients with ovarian cancer are more susceptible to acute kidney injury (AKI) due to the side effect of chemotherapy, tumour burden and metastasis which can cause obstruction or direct invasion of the urinary tract, impairing renal function. Moreover, cytoreductive surgery combined with cisplatin-based chemotherapy also puts patients at risk of developing AKI. This study investigates the molecular links between OC and AKI, conditions that share overlapping pathogenic mechanisms but remain poorly understood in their interconnectedness. The study Identified the common differentially expressed genes (DEGs) and explore their potential as therapeutic targets, identify common pathways. Further the potential of phytocompound reserpine was evaluated as dual action on AKI and OC via molecular docking and in vitro experimentation.

The results identified twelve common genes between OC and acute AKI, with five genes (MDM2, EZH2, CD44, CCL5, IL1B) shown to be druggable targets through molecular docking with a reserpine. Pathway enrichment revealed shared involvement in signalling pathways regulating cell proliferation and repair. Reserpine exhibited selective cytotoxicity against ovarian cancer cells (SKOV3) without affecting kidney cells (HEK) in vitro and studied their anti-migratory properties on SKOV3 cells. These findings support a dual-target therapeutic approach that simultaneously mitigates tumour progression and renal injury in ovarian cancer patients, offering a promising strategy to improve both oncological outcomes and renal protection.

Keywords: Anti-migratory, cytotoxicity, biological functions, differentially expressed genes, Docking, druggable targets, MTT, Pathway analysis.

1.0 Introduction

OC remains a critical cause of female cancer mortality globally, primarily due to its late-stage diagnosis and complex tumour biology. Despite advances in therapy, comorbid conditions significantly contribute to the clinical burden and patient outcomes. Among these, renal impairment has emerged as a frequent and clinically relevant complication in OC patients even at diagnosis, affecting nearly a third of cases in some cohorts. This co-occurrence reflects a multifactorial interplay of pathophysiological processes, including tumour-related urinary tract obstruction, metabolic disturbances, and systemic inflammation [1].

According to a study by Donadio et al., renal impairment is common in patients with newly diagnosed ovarian cancer, with 28% exhibiting reduced glomerular filtration rate (GFR) below 60 ml/min/1.73 m^2, a threshold relevant to chemotherapy eligibility. Additionally, 18% of patients showed morphological kidney alterations, predominantly moderate to severe dilation of the upper urinary tract. These functional and structural renal changes occur independently of tumour stage or prior kidney disease and are not explained by age-related decline alone. Therefore, early evaluation of renal function and morphology is essential in OC patients to guide optimal treatment decisions and manage potential renal complications effectively [2].

1.1 Reserpine: promising candidates for dual action potential in OC and AKI

Phytochemicals have emerged as promising candidates for both OC and AKI via different mechanisms. Reserpine has shown promise in OC by inhibiting STAT3 and NF-κB signalling, key pathways linked to drug resistance and tumour survival. It can trigger Reactive oxygen species (ROS) generation, mitochondrial dysfunction, and caspase activation, leading to apoptosis. By downregulating Bcl-2 and upregulating Bax, reserpine promotes cancer cell death, suggesting its potential as a chemosensitizer in resistant OC therapy. Reserpine also has a role in reducing AKI and can reduce cisplatin-induced AKI by protecting kidney cells from damage and lowering inflammation. Studies have demonstrated that it decreases serum creatinine and blood urea nitrogen levels, improves kidney tissue structure, and reduces oxidative stress and cell death. Overall, reserpine helps preserve kidney function and prevents the nephrotoxic effects caused by cisplatin treatment [3].

1.2 Integration of Genomic Data, Protein-Protein Interaction Networks, and In Silico Molecular Docking: A Comprehensive Approach to Understanding Disease Mechanisms

The integration of Gene Expression Omnibus (GEO) datasets, protein-protein interaction (PPI) networks, and in silico molecular docking provides a comprehensive framework to understand complex disease mechanisms. GEO datasets offer extensive gene expression profiles that enable identification of DEGs across pathological conditions, forming the basis for molecular insights [4].

PPI networks constructed using databases like STRING, help visualize molecular interactions, revealing hub proteins that are critical therapeutic targets. Combining PPI with transcriptomic data allows identification of dysregulated pathways and functional modules. In silico molecular docking further complements this by predicting the interactions between potential drug compounds and target proteins, aiding drug design. Together, these approaches accelerate the discovery of effective therapies by integrating molecular data with structural biology insights. Molecular docking helps in understanding the protein-ligand complex, providing insights into the stability of protein-ligand complexes and their pharmacokinetic properties. Together, these approaches improve and accelerate the discovery of effective therapies by integrating molecular data with structural biology insights [5].

Identifying common therapeutic targets in OC and AKI may enable strategies that simultaneously suppress tumor progression while protecting renal function. Therefore, this study has been undertaken to explore shared OC–AKI pathways and evaluated reserpine as a potential multi-target modulator using integrated bioinformatics and experimental studies.

2.0 Material and methods

2.1 Differentially expressed genes

DEGs were identified from publicly available GEO datasets, specifically GSE18520, which profiles whole-genome expression in papillary serous ovarian adenocarcinomas, and GSE139061, which were transcriptomic signatures of kidney injury in human renal biopsy specimens. The Genes exhibiting statistically significant changes were filtered based on a p-value threshold of less than 0.05 and an absolute log fold change >0.5. Subsequently, these filtered gene sets were compared using Venny 2.0 software to identify overlapping and common genes in both datasets, thereby highlighting shared molecular pathways and networks between OC and AKI.

2.2 Construction of Protein-Protein interaction network

The common DEGs were analysed using the STRING database to construct a PPI network, applying a high confidence score threshold of 0.7 to ensure reliable interactions. The resulting PPI network, reflecting the interactions among genes identified by Venny 2.0, was then imported into Cytoscape for detailed visualization and analysis. Separate interactome networks for AKI and OC were also created and merged to identify overlapping nodes, representing shared human protein partners involved in both conditions, thereby revealing critical molecular crosstalk during their co-occurrence.

2.3 Analysis of PPI and hub bottlenecks common in AKI and Ovarian cancer

The merged protein-protein interaction (PPI) subnetwork was imported into Cytoscape and analyzed using the Network Analyzer plugin, which computed key topological features. Further, the CytoHubba plugin was utilized to explore and predict critical nodes and subnetworks within the network by evaluating centrality measures such as degree, bottleneck genes, eccentricity, closeness, radiality, and betweenness each based on shortest path calculations.

2.4 Network clustering

Clustering of the AKI and OC, PPI networks was performed using the MCODE plugin in Cytoscape. MCODE identifies protein complexes, referred to as clusters, by detecting densely connected regions within the PPI network. For this study, only interactomes with an MCODE score greater than 3 were considered, ensuring the focus was on highly interconnected and potentially functionally significant protein clusters.

2.5 Target predictions of the compound reserpine

The target predictions of reserpine were done using Swiss Target Prediction online server where the compound smiles were retrieved from NCBI PubChem and were added to Swiss Target and the targets were further downloaded and used for molecular docking.

2.6 Molecular docking

The 3-dimensional structures of the proteins were downloaded using alpha fold online tool and Protein database (PDB) and the ligand structures as 3D-SDF were downloaded using PubChem database. The molecular docking was done using CB-dock an online tool, which is based on the AutoDock Vina algorithm, and the results were further analysed.

2.7 Identification of druggable targets

The druggable targets and proteins for AKI and OC was done using Therapeutic target database (TTD) and the targets that were found to be druggable were selected.

2.8 Gene ontology and pathway analysis

The functions like biological functions, gene ontology, enrichment and pathway analysis were done using ShinnyGo 0.85 tool which gave the detailed analysis of all the genes and the pathways that expressed.

2.9 Cell Culture and maintenance

Human ovarian cancer cells (SKOV3, epithelial ovarian cancer cell line) and human embryonic kidney cells (HEK-293) were obtained from the National Centre for Cell Sciences (NCCS), Pune, India. SKOV3 cells were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS), 0.1% penicillin–streptomycin–gentamicin antibiotic mixture, and 0.1% amphotericin-B antifungal solution, and maintained under standard culture conditions (37 °C, 5% CO_2).

HEK-293 cells were maintained in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum, 500 µg/mL penicillin–streptomycin–gentamicin, and 0.1% amphotericin-B under same incubation conditions (37 °C, 5% CO_2).

2.10 In vitro validation using MTT assay

Cells were seeded in 96-well plates at density of 1×10^4 cells/well in 96 well plate for SKOV3 and HEK-293 cells were seeded at density of 2×10^3 cells/well in 96 well plate for 24 hrs, post treatment with reserpine 20 µL MTT reagent was added and incubated for 3-4 hrs. The mitochondrial dehydrogenase in viable cells converts the yellow MTT to insoluble purple formazan crystals. These crystals were then dissolved in DMSO, and absorbance was measured at 570 nm, providing a quantitative measure of metabolically active cells.

2.11 Anti-migratory assay

The anti-migratory effect of reserpine was evaluated using a wound healing (scratch) assay. SKOV3 cells were seeded in 6-well dishes at a density of 3×10^5 cells/well and were allowed to attach and reach 80% sub confluency. The culture medium was then aspirated, and a uniform scratch was carefully created across the cell layer using a sterile pipette tip. The wells were gently washed with PBS to remove detached cells and debris, followed by the addition of fresh medium containing reserpine to the treatment group, while control wells received drug-free medium. Images of the wound area were captured at 0, 24, and 48 hrs using an inverted microscope, and cell migration was assessed by measuring the rate of wound closure in treated wells compared to controls.

https://doi.org/10.1051/bioconf/202623301015

3.0 Results and discussion

3.1 Identification of DEGs and construction of PPI

The volcano plots of GSE18520 OC and GSE139061 AKI were plotted with the help of GEO2R, these volcano plots showed the upregulated and downregulated genes in the following datasets shown (Fig 1).

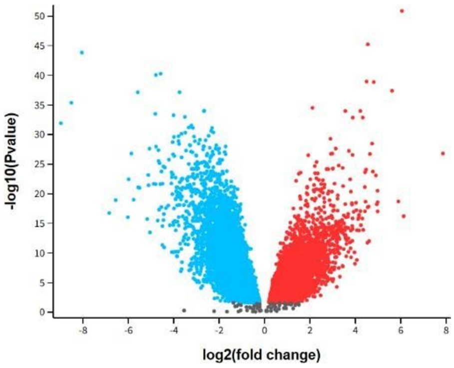


Fig 1: Volcano plots of OC and AKI showing upregulated and downregulated genes.

The OC and AKI datasets were obtained from GEO database to identify the common and overlapping genes present in both the datasets. A total of 2193 genes and proteins of ovarian carcinoma and 4963 of kidney injury were obtained from GEO database after filtering with log2fold value >0.5.

A network of all the 356 common genes and proteins between AKI and OC genes was made with high confidence of 0.7. The PPI network (Fig 2), it showed the interaction of many different proteins that interacted and were interconnected with each other. The network showed 437 unique protein nodes, that demonstrated the complexity and the broadness of the network by involving the relevant proteins that play roles in various molecular mechanisms.

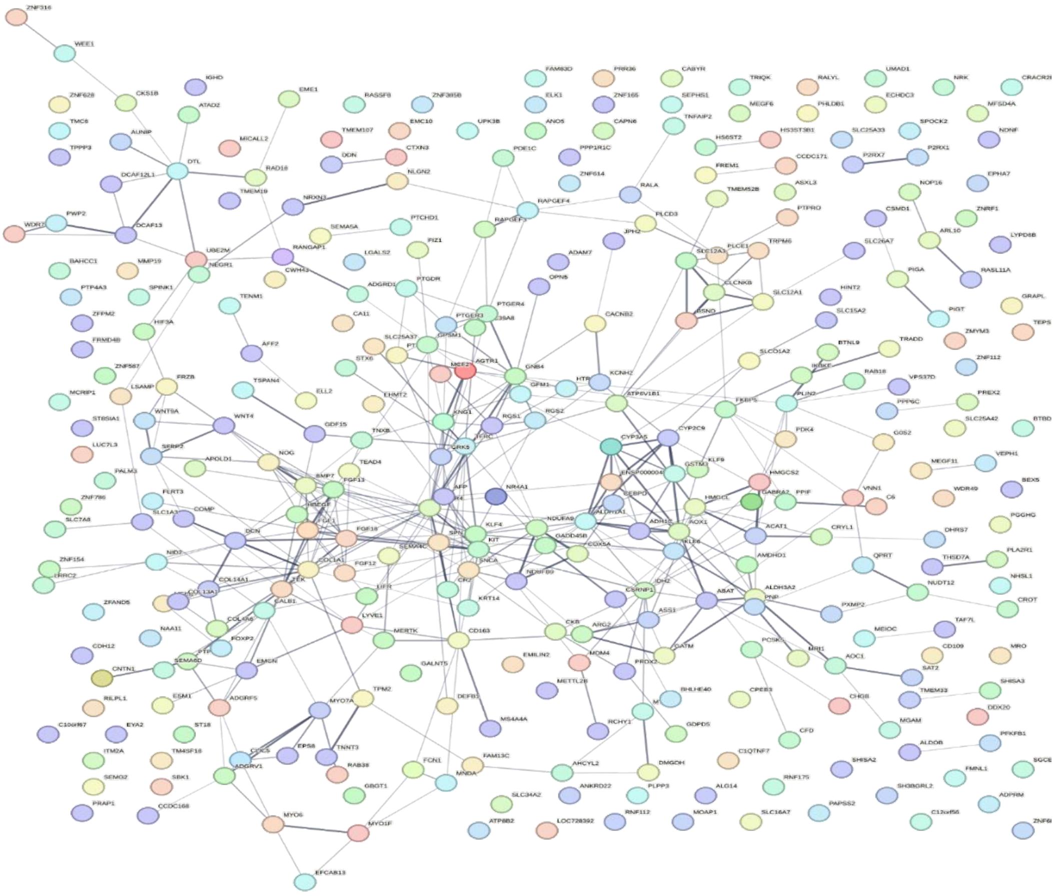


Fig 2: PPI network of common genes in AKI and OC.

3.2 Analysis of DEGs in cystoscape and identification of common genes

Clusters with high MCODE scores that is >3 were selected, where 21 clusters represented functional diversity and modularity within the network and ranging multiple biological conditions. Analysis via Cytohubba plugin elucidated the top rank nodes as the hubs in the network creating the highest influence. Common DEGs identified in this study MDM2, EZH2, CD44, CCL5, and IL1B, which are involved in cell cycle control, epigenetic regulation, and inflammatory signaling, linking tumor progression with renal injury, the genes and their functions are mentioned in Table 1.

Table 1: the list of common genes, their functions and mechanisms.

Gene Symbol	Main Role / Function	Implicated Mechanisms	References
MDM2	Regulator of p53 and cell cycle	Cell proliferation, DNA damage response	[6]
GNAQ	G protein signaling	Signal transduction	[7]
E2F1	Transcription factor controlling cell cycle	Cell cycle regulation	[8]
CD44	Cell adhesion molecule	Cell migration, immune cell interaction	[9]
CCL5	Chemokine involved in immune cell recruitment	Immune response, inflammation	[10]
CDT1	DNA replication licensing factor	DNA replication, proliferation	[11]
EZH2	Epigenetic regulator	Gene expression modulation, proliferation	[12]
STX1A	Vesicle fusion regulator	Cellular trafficking	[13]
CDC45	DNA replication initiation factor	DNA replication	[14]
RECQL4	Genome stability helicase	DNA repair, genome maintenance	[15]
CACNG4	Calcium channel auxiliary subunit	Calcium signalling	[16]
IL1B	Pro-inflammatory cytokine	Inflammation, immune response	[17]

3.3 Network-Based common target screening and mechanistic evaluation of reserpine via docking and pathway enrichment

Reserpine targets were predicted using Swiss Target Prediction and compared with common genes from network analysis, identifying MDM2 and EZH2 as overlapping targets. Screening through the TTD revealed five potential druggable proteins (Table 2). Molecular docking using CBDock showed strong binding affinity of reserpine with EZH2 (−9.1 kcal/mol) and CD44 (−8.9 kcal/mol) (Fig 3), suggesting good docking scores and potential of reserpine in binding to these proteins and its therapeutic potential in both AKI and OC.

The in-silico analysis indicates that reserpine interacts with the shared OC-AKI molecular network through binding to EZH2 and MDM2. The favorable docking affinity toward EZH2 suggests modulation of epigenetic regulation and p53-mediated stress signaling, mechanisms central to OC progression. Additionally, its interaction with CD44 supports a potential role in regulating inflammatory and cell-adhesion pathways, which may contribute to attenuation of inflammation associated with AKI [18].

Functional clustering and pathway enrichment analyses revealed shared mechanisms between AKI and OC, with Hippo, Wnt, calcium signaling, ECM–receptor interaction, and focal adhesion pathways forming a central regulatory network. In OC, these pathways drive tumor cell proliferation, survival, invasion, and metastatic dissemination, whereas in AKI they regulate tubular cell apoptosis, regeneration, inflammatory responses, and post-injury tissue remodeling (Fig 4). Additional pathways including insulin signaling, GnRH secretion, glutamatergic and sphingolipid signaling were also identified but were less central to the shared disease pathology [19].

Table 2: The druggable proteins, functions and in silico docking scores with reserpine

S.NO	Name of the druggable protein	Function	Docking score with reserpine
1.	EZH2: Enhancer of zeste homolog 2 (histone-lysine N-methyltransferase)	Catalyses histone methylation, silencing genes involved in development and cancer.	-9.1
2.	MDM2: E3 ubiquitin-protein ligase MDM2	Regulates p53 by targeting it for degradation, controlling cell cycle and apoptosis.	-7.3
3.	CD44: CD44 antigen (Homing cell adhesion molecule)	Cell adhesion molecule involved in cell migration and immune response.	-8.9
4.	CCL5: C-C motif chemokine ligand 5	Chemokine that attracts immune cells to sites of inflammation.	-6.6
5.	IL1B: Interleukin-1 beta	Pro-inflammatory cytokine mediating immune response and inflammation.	-7.4

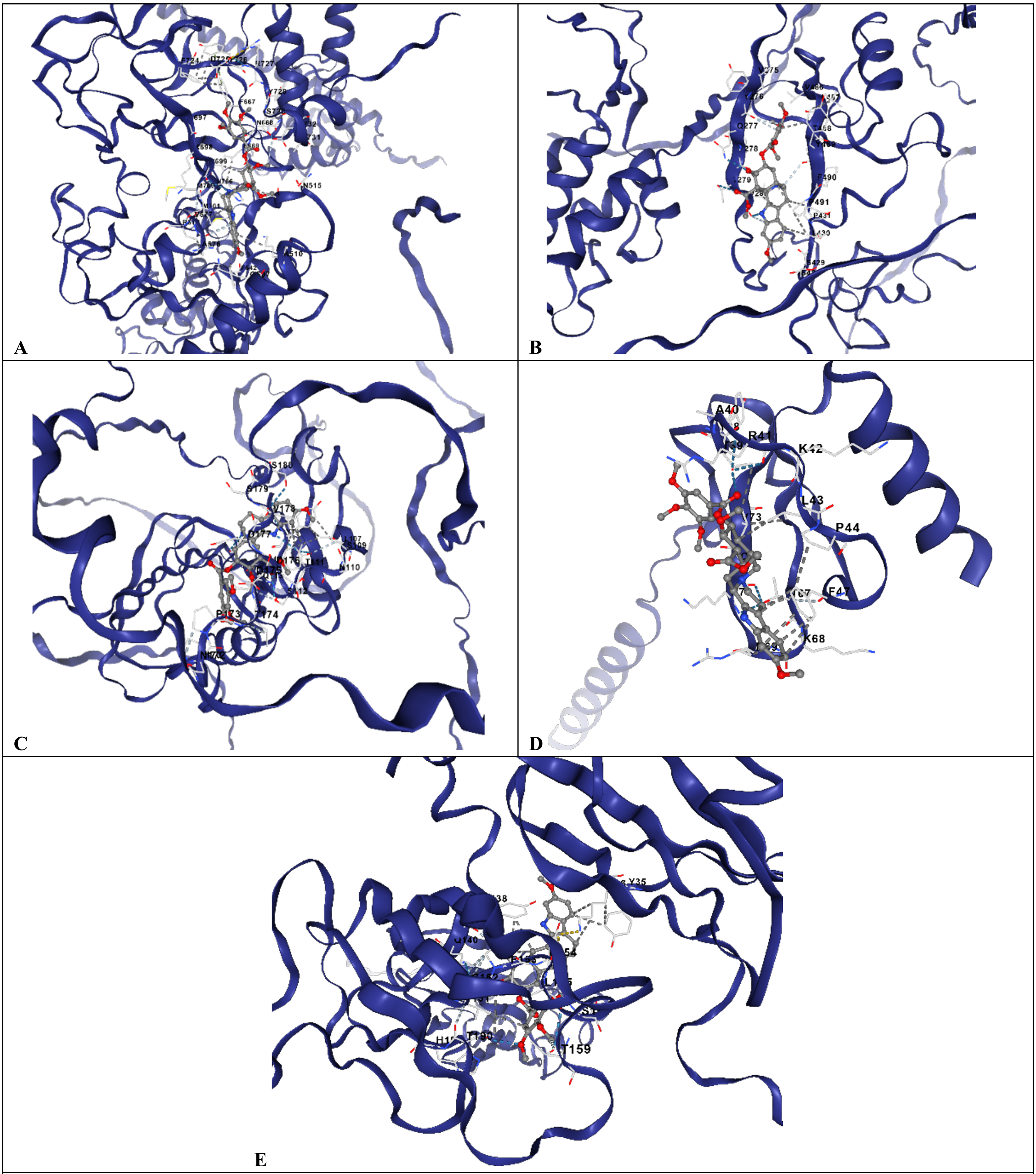


Fig 3: Reserpine interaction with shared molecular targets of AKI and OC. (A) Reserpine interaction with MDM2, (B) Reserpine interaction with EZH2, (C) Reserpine interaction with CD44, (D) Reserpine interaction with CCL5, (E) Reserpine interaction with IL-1B

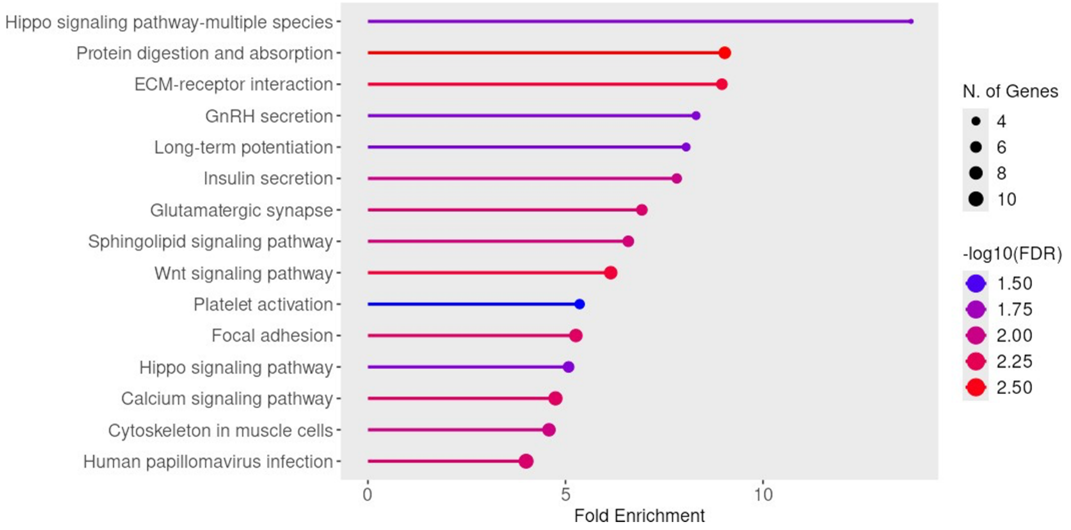


Fig 4: major pathways associated with common genes.

3.4 Validation of cell viability inhibition by reserpine on SKOV3 ovarian cancer cells and safety analysis on HEK-293 cells

3.4.1 Reserpine-Induced Inhibition of cell Viability in SKOV3 Ovarian Cancer Cells

Treatment with reserpine reduced cell viability in a concentration-dependent manner (Fig 5), with calculated IC_{50} of 125 µM on SKOV3 cells.

EZH2 is the catalytic subunit of PRC2 (Polycom repressive complex 2) and mediates epigenetic silencing. Its overexpression is linked to aggressive growth, metastasis, and poor prognosis in ovarian cancer. Strong docking affinity of reserpine toward EZH2 suggests potential interference with epigenetic regulation in SKOV3 cells. Since EZH2 inhibition reduces proliferation and induces apoptosis in ovarian cancer models, the decreased viability observed at 125 µM may partly result from disruption of EZH2-driven transcriptional repression [20].

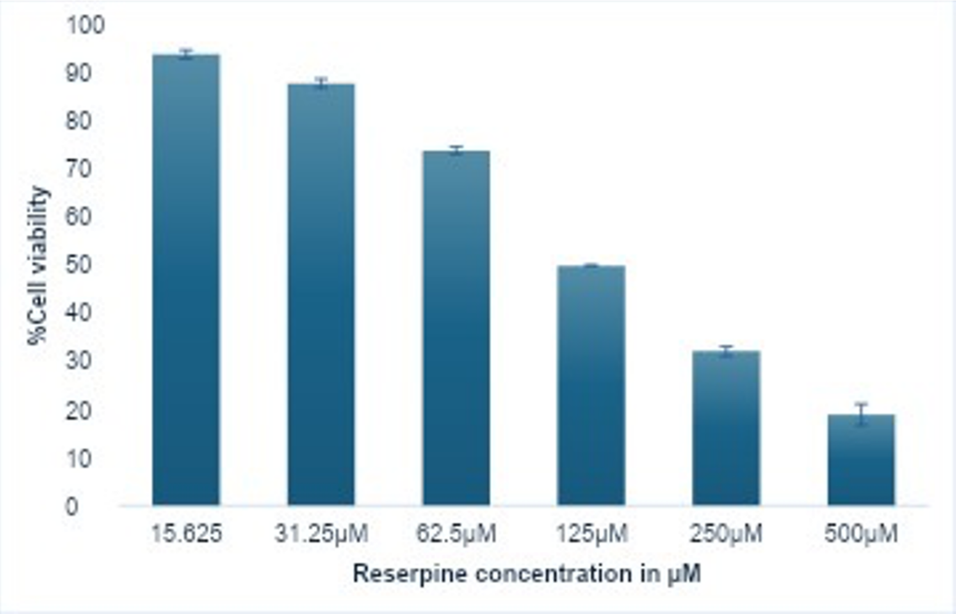


Fig 5: The effect of reserpine in SKOV3 cells.

3.4.2 Safety analysis on HEK-293 cells

Reserpine exhibited minimal toxicity toward HEK293 cells (Fig 6), where in at 125 µM (the IC_{50} concentration for SKOV3 cells), cell viability remained high at 99.8%, indicating safety at the effective anticancer dose. At the highest tested concentration (1 mM), cell viability remained approximately 74%, indicating minimal cytotoxicity in HEK-293 cells. This differential response suggests that reserpine preferentially targets cancer cells while maintaining relative safety in normal kidney cells, supporting its potential dual role as an anticancer and nephroprotective agent.

The high viability observed in HEK-293 cells in our study indicates preservation of normal renal cellular integrity. Consistently, docking showed interactions with inflammatory mediators (CCL5 and IL1B), suggesting modulation rather than suppression of physiological immune activity. This aligns with studies that reserpine attenuates AKI via inhibition of NF-κB and cGAS–STING inflammatory signaling. Together, our experimental and in-silico findings support a potential renoprotective effect alongside its anticancer activity [21].

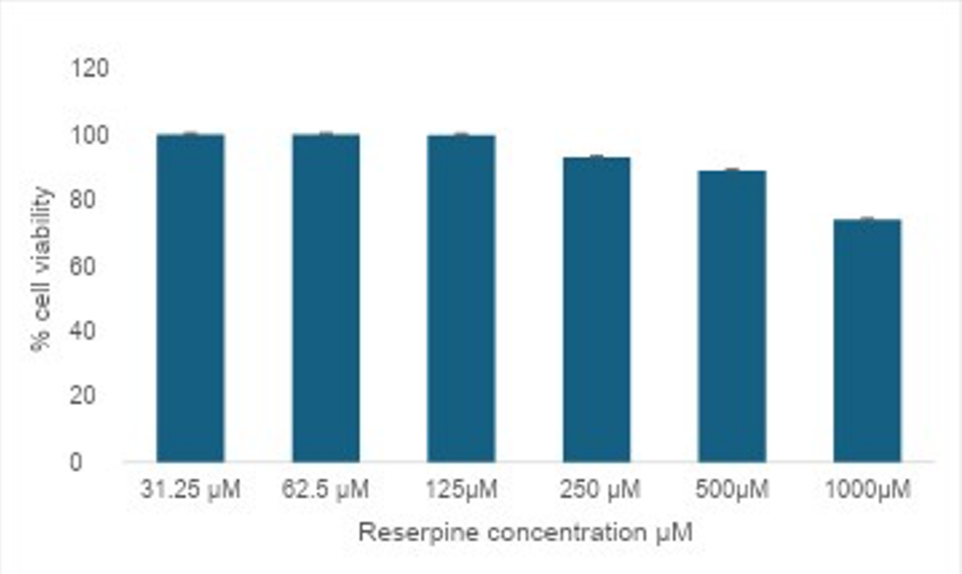
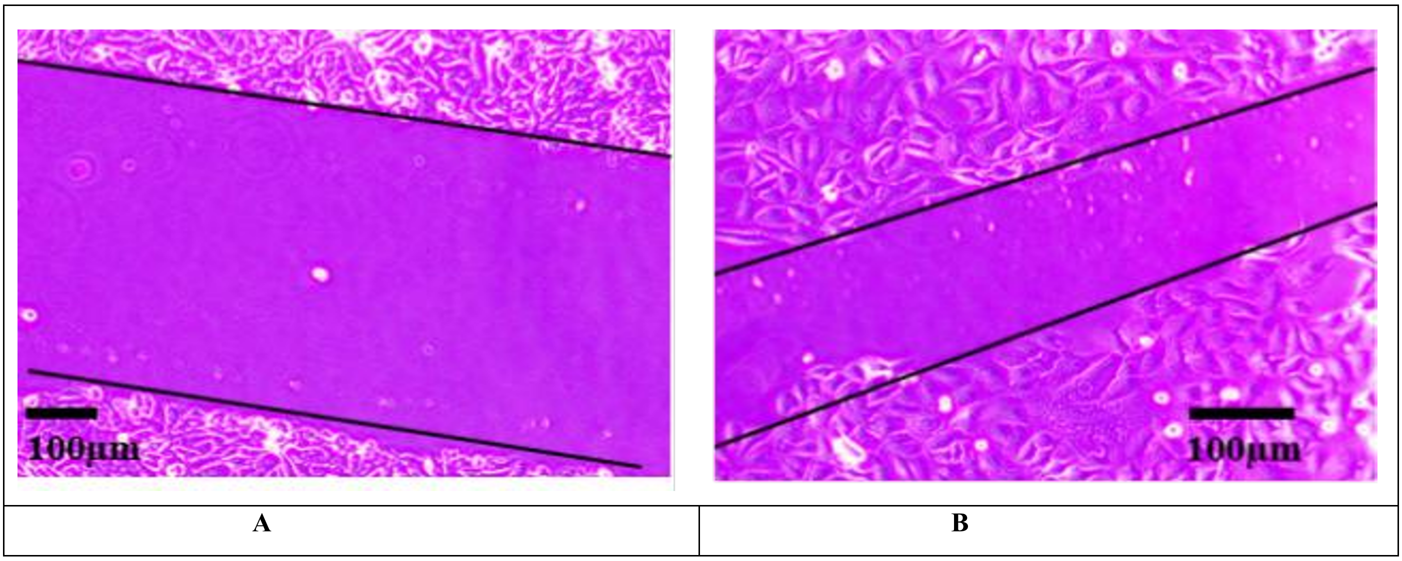


Fig 6: Safety analysis of reserpine on HEK-293 cells.

3.5 Anti-migratory effects of Reserpine on Skov3 cells

Reserpine significantly reduced the migratory capacity of SKOV3 cells at 125 µM. In the untreated control, approximately 80% of the wound area was closed after 48 h, whereas only 36% closure was observed in the reserpine-treated group, indicating marked inhibition of cell migration (Fig 7).



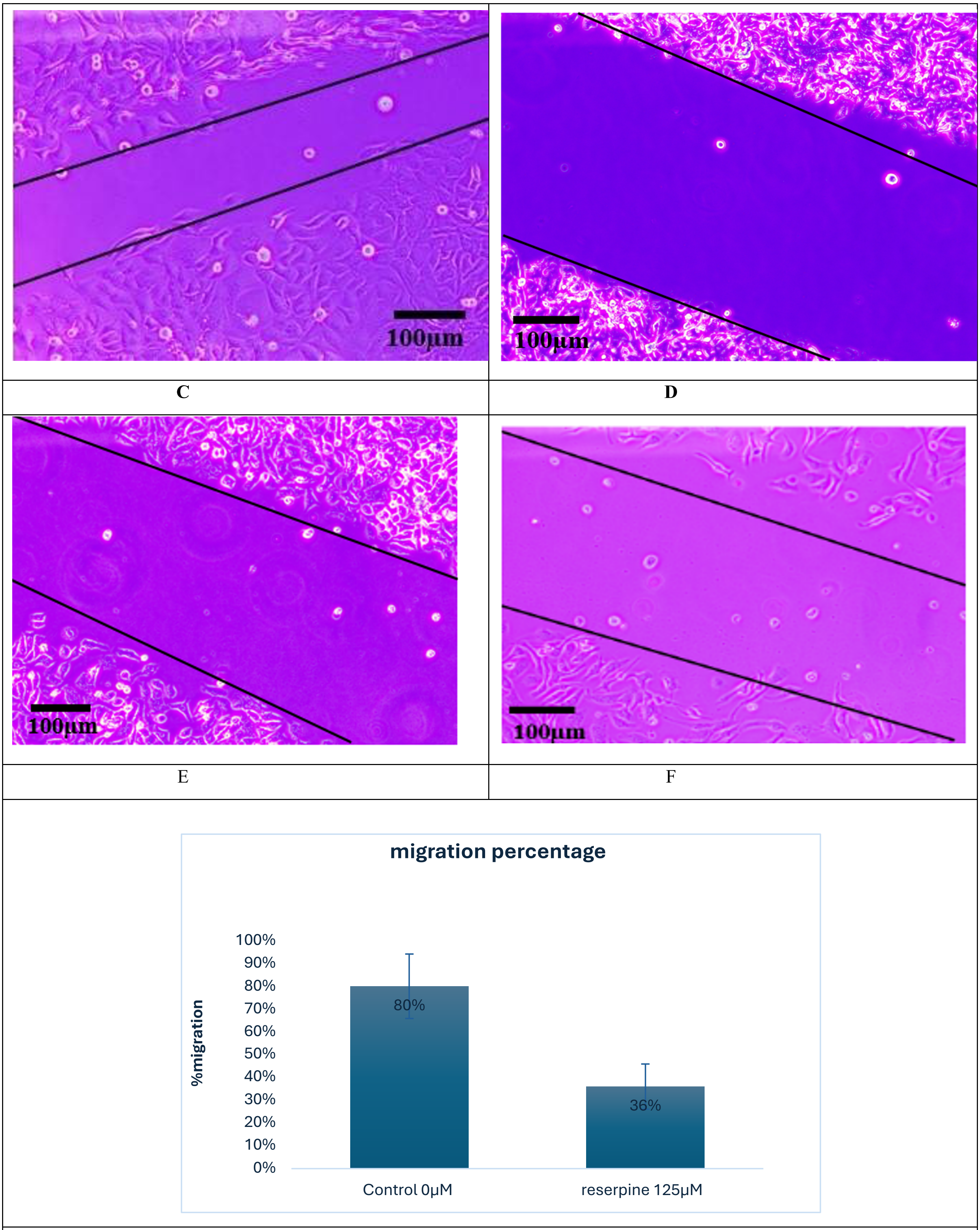


Fig 7: Comparative analysis of reserpine treatment and no treatment (Control) on wound healing capacity on SKOV3 cells at (A) 0 hr Control (B) 24 hrs control, (C) 48 hrs control, (D) 0 hrs post reserpine treatment, (E) 24 hrs post reserpine treatment, (F) 48 hrs post reserpine treatment, (G) Comparison of wound closure (%) between control and reserpine treatment.

Reserpine reduced SKOV3 migration in the wound healing assay, indicating inhibition of metastatic behavior. This aligns with docking results showing strong interaction with CD44 and EZH2 and moderate binding to MDM2, proteins involved in adhesion and survival. Pathway enrichment further supported targeting of focal adhesion, ECM receptor interaction, and Wnt/Hippo signaling. Together, these findings suggest multi-target modulation consistent with the observed functional effects [22].

5.0 Conclusion

In conclusion, this study revealed molecular crosstalk between AKI and OC, identifying 12 shared genes, including MDM2, EZH2, CD44, CCL5, and IL1B. Among these, MDM2 and EZH2 were predicted targets of reserpine with strong docking affinity (−9.1 kcal/mol for EZH2; −8.9 kcal/mol for CD44), and five proteins were identified as druggable targets. Enrichment analysis highlighted key pathways such as Hippo, Wnt, ECM remodeling, and focal adhesion, indicating shared pathogenic mechanisms.

In vitro, reserpine inhibited growth of SKOV3 cells in a dose-dependent manner (IC_{50} = 125 µM) and markedly reduced cell migration, while preserving viability in HEK-293 cells. These findings demonstrate selective anticancer activity alongside maintenance of normal renal cell integrity, supporting its potential as a dual-acting agent with anticancer and renoprotective properties and warranting further investigation.

List of abbreviations

AKI – Acute kidney injury

Bax – Bcl-2 associated x protein

Bcl-2 – B-cell lymphoma 2

CACNG4 – Calcium voltage-gated channel auxiliary subunit gamma 4

CCL5 – C-c motif chemokine ligand 5

CDC45 – Cell division cycle 45

CD44 – Cd44 antigen (homing cell adhesion molecule)

CDT1 – Chromatin licensing and dna replication factor 1

DEGs – Differentially expressed genes

DMEM – Dulbecco's modified eagle medium

E2F1 – E2f transcription factor 1

ROS – Reactive oxygen species

STAT3 – Signal transducer and activator of transcription 3

STX1A – Syntaxin 1a

EZH2 – Enhancer of zeste homolog 2 FBS – Fetal bovine serum

GEO – Gene expression omnibus

GFR – Glomerular filtration rate

GNAQ – G protein subunit alpha q

HEK-293 – Human embryonic kidney 293 cells

IL1B – Interleukin-1 beta

MDM2 – Mouse double minute 2 homolog (e3 ubiquitin-protein ligase mdm2)

MTT – 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay

NF-κB – Nuclear factor kappa-b

OC – Ovarian cancer

PPI – Protein–protein interaction

RECQL4 – Recq like helicase 4

TTD – Therapeutic target database

Funding

No specific funding support for this work.

Credit authorship contribution statement

Saloni Joshi: Writing, editing of original drafts

Reema Gabrani: Editing, reviewing, supervision, and validation of the original draft

Ruby Beniwal: Editing, reviewing, and supervision.

Declaration of Competing Interest

The authors declare no competing financial or non-financial interests that could have influenced the work reported in this review article.

Acknowledgments

The authors would like to provide their acknowledgments to the Jaypee Institute of Information Technology for infrastructure facilities and support.

Declaration of Generative AI and AI-assisted technologies in the writing process

The author used AI tools to correct grammar and improve the quality of writing and paraphrasing and enhance the quality of images.

Data availability

GSE18520, GSE139061 datasets were used.

References

[1] Taylor AH, Ayakannu T. Renal Dysfunction in Gynaecological Cancers. Ann Med Clin Oncol 2024;7:161. https://doi.org/10.29011/2833-3497.000161.

[2] Donadio C, Lucchesi A, Ardini M, Cosio S, Gadducci A. Renal impairment in patients with ovarian cancer. European Journal of Obstetrics & Gynecology and Reproductive Biology 2003;106:198–202. https://doi.org/10.1016/S0301-2115(02)00234-8.

[3] Xu N, Mu R, Deng S, Han Y, Shi Y, Fu X, et al. Reserpine alleviates cisplatin-induced acute kidney injury via anti-ferroptosis and cGAS/STING pathway. Ren Fail 2024;46. https://doi.org/10.1080/0886022X.2024.2406395.

[4] Barrett T, Wilhite SE, Ledoux P, Evangelista C, Kim IF, Tomashevsky M, et al. NCBI GEO: archive for functional genomics data sets—update. Nucleic Acids Res 2012;41:D991–5. https://doi.org/10.1093/nar/gks1193.

[5] Chen Q, Mao Y, Cai S, Zhang X, Zeng C, Chen Q, et al. Integrated bioinformatics and molecular docking analysis reveal potential hub genes and targeted therapeutics in sepsis-associated acute lung injury. Front Immunol 2025;16. https://doi.org/10.3389/fimmu.2025.1684774.

[6] Wade M, Li Y-C, Wahl GM. MDM2, MDMX and p53 in oncogenesis and cancer therapy. Nat Rev Cancer 2013;13:83–96. https://doi.org/10.1038/nrc3430.

[7] Van Raamsdonk CD, Griewank KG, Crosby MB, Garrido MC, Vemula S, Wiesner T, et al. Mutations in GNA11 in Uveal Melanoma. New England Journal of Medicine 2010;363:2191–9. https://doi.org/10.1056/NEJMoa1000584.

[8] Sheldon LA. Inhibition of E2F1 activity and cell cycle progression by arsenic via retinoblastoma protein. Cell Cycle 2017;16:2058–72. https://doi.org/10.1080/15384101.2017.1338221.

[9] Ponta H, Sherman L, Herrlich PA. CD44: From adhesion molecules to signalling regulators. Nat Rev Mol Cell Biol 2003;4:33–45. https://doi.org/10.1038/nrm1004.

[10] Araujo JM, Gomez AC, Aguilar A, Salgado R, Balko JM, Bravo L, et al. Effect of CCL5 expression in the recruitment of immune cells in triple negative breast cancer. Sci Rep 2018;8:4899. https://doi.org/10.1038/s41598-018-23099-7.

[11] Nishitani H, Taraviras S, Lygerou Z, Nishimoto T. The Human Licensing Factor for DNA Replication Cdt1 Accumulates in G1 and Is Destabilized after Initiation of S-phase. Journal of Biological Chemistry 2001;276:44905–11. https://doi.org/10.1074/jbc.M105406200.

[12] Kim KH, Roberts CWM. Targeting EZH2 in cancer. Nat Med 2016;22:128–34. https://doi.org/10.1038/nm.4036.

[13] Zhou Q, Xiao J, Liu Y. Participation of syntaxin 1A in membrane trafficking involving neurite elongation and membrane expansion. J Neurosci Res 2000;61:321–8. https://doi.org/10.1002/10974547(20000801)61:3<321::AID-JNR10>3.0.CO;2-L.

[14] Moyer SE, Lewis PW, Botchan MR. Isolation of the Cdc45/Mcm2–7/GINS (CMG) complex, a candidate for the eukaryotic DNA replication fork helicase. Proceedings of the National Academy of Sciences 2006;103:10236–41. https://doi.org/10.1073/pnas.0602400103.

[15] Luong TT, Bernstein KA. Role and Regulation of the RECQL4 Family during Genomic Integrity Maintenance. Genes (Basel) 2021;12:1919. https://doi.org/10.3390/genes12121919.

[16] Dolphin AC. Calcium channel auxiliary α2δ and β subunits: trafficking and one step beyond. Nat Rev Neurosci 2012;13:542–55. https://doi.org/10.1038/nrn3311.

[17] Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. Blood 2011;117:3720–32. https://doi.org/10.1182/blood-2010-07-273417.

[18] Karni-Schmidt O, Lokshin M, Prives C. The Roles of MDM2 and MDMX in Cancer. Annual Review of Pathology: Mechanisms of Disease 2016;11:617–44. https://doi.org/10.1146/annurev-pathol-012414040349.

[19] Xue C, Chu Q, Shi Q, Zeng Y, Lu J, Li L. Wnt signaling pathways in biology and disease: mechanisms and therapeutic advances. Signal Transduct Target Ther 2025;10:106. https://doi.org/10.1038/s41392-02502142-w.

[20] Rao Z-Y, Cai M-Y, Yang G-F, He L-R, Mai S-J, Hua W-F, et al. EZH2 supports ovarian carcinoma cell invasion and/or metastasis via regulation of TGF-β1 and is a predictor of outcome in ovarian carcinoma patients. Carcinogenesis 2010;31:1576–83. https://doi.org/10.1093/carcin/bgq150.

[21] Raguraman S, Almoallim HS, Alahmadi TA, Hussein-Al-Ali SH, Bharathi M, Ramu AK. Reserpine Induces Apoptosis in Drug-Resistant Cancer through Modulating STAT3 and NF-κB Signaling. Indian Journal of Pharmaceutical Education and Research 2024;58:s900–9. https://doi.org/10.5530/ijper.58.3s.91.

[22] Sohail A, Shams F, Nawaz A, Ain Q ul, Ijaz B. Antifibrotic potential of reserpine (alkaloid) targeting Keap1/Nrf2; oxidative stress pathway in CCl4-induced liver fibrosis. Chem Biol Interact 2025;407:111384. https://doi.org/10.1016/j.cbi.2025.111384.