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Original Article

Targeting PARP1 by Small Molecule Drugs for the Therapeutics of Gynaecological Cancers

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ABSTRACT

Background: In gynaecological cancers like ovarian, endometrial, and cervical cancer, where DNA damage repair mechanisms are frequently dysregulated, targeting PARP1 offers a targeted therapeutic approach. **Materials and Methods:** This study was aimed to identify the small molecules for the inhibition of PARP1 using bioinformatics and *in vitro* methods. Screening and molecular docking of a diverse ligand library identified Apigenin as a potential **Results:** PARP1 inhibitor, exhibiting strong binding affinity of -9.0 kcal/mol for the PARP1. Further analysis via SwissTargetPrediction revealed diverse biological activities associated with Apigenin, indicating its therapeutic potential. Additionally, time-dependent cytotoxicity assays demonstrated Apigenin's negligible effect on non-cancerous cells (HEK-293), affirming its safety profile. Moreover, relative mRNA expression studies in Apigenin-treated HeLa-229 cells revealed a significant decrease in PARP1 expression, suggesting its inhibitory effect on cancer-related pathways. **Conclusion:** Overall, these findings highlight Apigenin as a promising therapeutic cause for targeting PARP1 in cancer treatment, underscoring its potential for further preclinical and clinical investigations.

Keywords: Apigenin, Gynaecological Cancers, HeLa-229, Molecular Docking, PARP1, Inhibition.

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INTRODUCTION

Gynaecologic cancers include a variety of malignancies that have expressive impact the female reproductive system, such as uterine, vulvar, ovarian, and vaginal cancers.[1] These types of cancer collectively pose a significant global health challenge; in particular, ovarian cancer has high mortality rates.[2] Despite advancements in treatment methods, the prognosis for many gynaecologic cancers remains poor. Therefore, exploring new therapeutic approaches is essential. In recent years, targeting Poly polymerase 1 has emerged as a promising strategy for managing these malignancies due to its crucial role in a number of cellular procedures such as chromatin remodelling, DNA repair, and transcriptional regulation.[3] PARP1 inhibition indications to an accumulation of DNA damage especially in cells by imperfect homologous recombination repair mechanisms caused by BRCA mutations-this concept forms the basis for utilizing PARP1 inhibition as a therapeutic approach in cancer treatment.[4]

Gynaecologic cancers often have deficiencies in DNA repair mechanisms, making them vulnerable to synthetic lethality caused by PARP1 inhibition.[5] Ovarian cancers frequently contain BRCA1/2 mutations or other defects in the HR pathway, which makes them highly responsive to PARP inhibitors.[6] Increased expression of PARP1 has been perceived in various gynaecologic malignancies with ovarian, cervical and endometrial cancers.[7-9] This overexpression is linked to aggressive tumor behaviour, resistance to chemotherapy and poor clinical outcomes.[10] Targeting PARP1 presents a logical therapeutic strategy for disrupting vital cellular processes crucial for cancer cell survival and proliferation as it plays a role in tumor angiogenesis - crucial for tumor growth and metastasis.[11]

Platinum-based chemotherapy is a crucial part of the treatment for various gynaecologic cancers, yet the development of resistance presents significant challenge.[12] Preclinical studies indicate that PARP inhibition can overcome platinum resistance by increasing DNA damage and making resistant tumor cells more susceptible to chemotherapy-induced cytotoxicity.[13,14] Clinical trials have demonstrated strong clinical utility for PARP inhibitors in gynaecologic cancers, with robust preclinical evidence supporting their use.[15] Regulatory approval has been obtained for several PARPi, with olaparib, niraparib, rucaparib, and talazoparib, in the treatment of ovarian, fallopian tube, and peritoneal cancers.[16] These agents have shown effectiveness as monotherapy or as maintenance therapy following platinum-based chemotherapy and also hold potential in combination through other targeted agents or immunotherapy treatments.

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PARP inhibitors have completely changed how ovarian cancer is treated, offering new options for patients through recurrent or advanced disease. Maintenance therapy with PARPi after platinum-based chemotherapy has expressively lengthy progression-free survival in patients with BRCA-mutated tumors and those with homologous recombination deficiency.[17] Furthermore, PARP inhibitors have shown effectiveness in both platinum-sensitive and platinum-resistant disease settings, whether used only or in arrangement by anti-angiogenic agents or immunotherapy.[18] Currently, early-stage clinical trials are being now evaluating the ability of PARP inhibitors in cancer (cervical) as standalone treatment or when used alongside chemotherapy.[19] Initial findings indicate promising antitumor effects, particularly in patients with HRD tumors. Similarly, molecular profiling has identified patient subsets with DNA repair pathway defects making PARP inhibitors a viable option for targeted therapy in endometrial cancer.[20]

Targeting PARP1 is a rational and effective therapeutic strategy in gynaecologic cancers that exploits the concept of synthetic lethality to selectively eradicate tumor cells whereas parsimonious usual tissues. The success of PARP inhibitors in clinical practice underscores the importance of translational research in bridging bench-to-bedside advancements and improving patient outcomes.

MATERIALS AND METHODS

Structure homology modelling of protein and PARP1 receptor preparation

The structure (3D) of the target protein, PARP1, was modelled by available tool SwissModel. Briefly, the FASTA sequences of PARP1 was obtained from PubMed. The template sequences of homologous protein with known 3D- structures were searched using Protein Data Bank (PDB). Thereafter, we selected one suitable template structure for target protein (P09874.1.A) based on sequence correspondence, structure eminence, and biological significance. This template structure was used to model the structure of PARP1 using SWISSMODEL.[21-24] High resolution structure of PARP1 was retrieved from the Swiss-MODEL server (Figure 1a) and visualized using PyMOL and Chimera to analyse the structural features and properties. Preparing the receptors for molecular docking is a crucial step, regular receptor preparation protocol was monitored to refine the structure of PARP1.[25,26] The structure of PARP1 was inspected for any steric clashes, missing atoms, or unusual bond angles. The structures were assigned partial charges and atom types to the protein atoms using force field parameters suitable for molecular docking. The structures were finally saved in PDBQT format, a format compatible with the molecular docking.

Choosing ready ligands for PARP1 molecular docking

To assemble a diverse set of ligand molecules for virtual screening, a small library was curated from the database (DrugBank: https://go.drugbank.com/). This library comprised 23 entries encompassing US approved, experimental, and investigational nutraceutical small molecules, selected based on their relevance to the study's objectives. Subsequently, the 3D (three-dimensional) structures of these molecules (small) were obtained in SDF (Structure Data files) from the database (PubChem link: https://pubchem.ncbi.nlm.nih.gov/). Every SDF file felt a hard authentication process to ensure structural integrity. Bond lengths, bond angles, and torsional angles were meticulously scrutinized and corrected as necessary to rectify any discrepancies or irregularities. Following the validation and correction process, the structures of the ligand molecules were converted into the PDBQT format. This conversion facilitated compatibility with molecular docking software and ensured accurate representation of the ligand structures during subsequent docking simulations.

Screening and molecular docking

A comprehensive screening of 23 compounds was showed to assess their binding affinity alongside PARP1. Based on their binding affinities top hit was designated for advance MD (molecular docking) studies by using PARP1. The MD of top hit through PARP1 was performed using CB-Dock2, a server for protein-ligand docking (blind).[27] CB-Dock2 integrates various functionalities, including cavity detection, docking, and homologous template fitting, enabling accurate prediction of binding sites and affinity between proteins and ligands. This approach allows researchers to gain insights into the potential interactions between ligand and target molecule at the molecular level.

Extrapolation of Activity Spectra for Apigenin using SwissTargetPrediction tool

To explore the biological activity spectrum associated with Apigenin, we utilized the tool (SwissTargetPrediction), with link (http://www.swisstargetprediction.ch/). Tool is an *in silico* available platform specifically developed to expect potential targets for small molecules or drugs. The SwissTargetPrediction tool operates by analysing the chemical structure of a compound, typically represented in SMILES notation, and predicting potential protein targets based on structural resemblances and known ligand-protein interaction arrangements.

Cell viability Test by MTT assay on conc.based manner

In a 96-well microplate, cells (HEK-293) were seeded at a density of 5,000 cells per well and cultured for 24 hr in a CO_2 incubator machine. Subsequently, they exposed cells to altered concentrations of Apigenin (0-100 μM) for a duration of 72

hr in order to assess the impact of this drug on the viability of cells.[28] After completion of treatment period, media was replaced with 100 µL of new medium inclosing 0.5 mg/mL of MTT reagent and plate was incubated for 4 hr in dark. MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide) containing medium was aspirated, and 100 µL of Dimethyl Sulfoxide (DMSO) was additional to every well to thaw the formazan crystals through gentle agitation for 10 min. The absorbance of the formazan solution was calculated at 570 nm via a plate reader. Practically Cell viability was then measured through dividing the net absorbance of the test wells by that of the control wells (untreated cells) and multiplying the result thru 100.

Time-dependent Cell viability using MTT assay

Apigenin (purity ≥95.0% HPLC) was procured from Sigma (CAS No: 520-36-5). HEK-293 (human embryonic kidney) cell line was gotten from the NCCS (National Center for Cell Sciences), Pune, India. HEK-293 cells were cultured and maintained in Dulbecco's Modified Eagle Medium (DMEM) added with 10% Fetal Bovine Serum (FBS) and 1% antibiotics. A 96well microplate was used, and 5,000 cells per well were seeded into each well. After reaching the confluency, cells were treated with Apigenin 50 µM for 12, 24, 36, 48, 60, and 72 hr' time dependent manner.[28] After completion of treatment period, media was replaced with 100 µL of new medium keeping 0.5 mg/mL of reagent (MTT) and plate was incubated for 4 hr in dark. MTT-containing medium was aspirated, and 100 µL of DMSO was added to every well to thaw the formazan crystals through gentle agitation for 10 min. The absorbance of the formazan solution was measured at 570 nm using a plate reader. Cell viability was then deliberated by dividing the net absorbance of the test wells by that of the control wells (untreated cells) and multiplying the result via 100.

Relative mRNA expression of PARP1 in Apigenin treated HeLa-229 cells

To examine the outcome of µM 50 Apigenin on PARP1 gene expression, HeLa-229 cells were treated for the duration of 48 hr. Consequently, RNA extraction was conceded out via QIAwave RNA Mini Kit (Quigen) conferring to the maker's directions. The take-out RNA was then subjected to cDNA synthesis via the cDNA Synthesis Kit (Quigen). Quantitative real-time Polymerase Chain Reaction (qRT-PCR) was did via Master Mix (SYBR™ Green) with brand (Thermo Fisher Scientific, USA) on RT-PCR System (Applied Biosystems). The expression level of the aim gene, PARP1, was evaluated and normalized to that of the housekeeping gene GAPDH. The relative fold change in PARP1 expression was measured via the $2^{-\Delta\Delta CT}$ technique. The sequences (primer) utilized were as follows: PARP1: forward 5'-AAGGCGAATGCCAGCGTTAC-3' and reverse 5'-GCACTCTTGGAGACCATGTCA-3', GAPDH: forward 5'-GGCCTCCAAGGAGTAAGACC-3' and reverse 5'CTGTGAGGAGGGGAGATTCA-3'.[29]

RESULTS

Homology modelling and research of PARP1

Figure 1A demonstrates the alignment of sequence with the template structure. Figure 1B shows the structure (high-resolution) of the PARP1 model obtained through Swiss-MODEL. The model boasts a remarkable sequence identity and coverage of 100%, indicating a clear-cut alignment thru the target sequence. Notably, the excellence valuation of the model reveals excellence, as evidenced by a GMQE (Global Model Quality Estimation) score of 0.82. These scores, going between 0 and 1, provide an overall evaluation of model class, through higher values reflecting more anticipated class. It's essential to note that while GMQE is coverage-dependent, meaning it considers the alignment coverage of the model, QMEANDisCo evaluates model quality independently of explicit coverage dependency. Figure 1C depicts the Ramachandran Plot of the modelled structure, offering a visualization of enthusiastically favoured regions for the backbone dihedral angles of amino acid residues within the protein structure.

Screening and Molecular Docking (MD) shown Apigenin as probable inhibitor of PARP1

Screening indicated Apigenin as top hit and underwent MD against the target protein PARP1. The outcomes of the docking process, are visually represented in Figure 2A-C. The docked complex revealed a binding affinity of -9.0 kcal/mol between Apigenin and PARP1. Figure 2A represents a cartoon presentation of the PARP1: Apigenin complex, offering insights into the spatial preparation of the molecules, while Figure 2B presents a surface view of the complex, offering additional perspectives on their interaction. Figure 2C represents a 2D interaction of the protein-ligand complex.

Evidence of the fruitful docking of Apigenin into the cavernous binding cavity of PARP1 is apparent from the docking pose. Apigenin formed hydrogen bonds with the ASP743 and GLU690 amino acid residues of PARP1. In addition to hydrogen bonds, variety of other interactions were observed between apigenin and PARP1. These interactions focus the complete nature of the binding between Apigenin and PARP1.

Swiss Target Prediction analysis

The SwissTargetPrediction analysis revealed wide range of biological activities associated with Apigenin (Figure 3). These outcomes collectively suggest that Apigenin holds promise as a potential therapeutic candidate, especially in its ability to target the activity of enzymes including cytochrome p450, hydrolases, kinases, nuclear receptors, Family A G protein-coupled receptors, oxidoreductases, and other cytosolic proteins.

Concentration dependent and Time interval cytotoxic effect

Figure 4A depicts the conc.-dependent effect of Apigenin on HEK-293 cell viability. Exploration publicized no significant conc.-dependent impact on cell viability, suggesting Apigenin lacks prominent belongings within the tried concentration range on these cells. Figure 4B illustrates the results of influence of Apigenin on the viability of HEK-293 cells in timedependent manner. HEK-293 cells were treated with IC_{50} concentration of Apigenin for 12, 24, 36, 48, 60, and72 hr, Outcomes revealed that regardless of the duration of exposure to Apigenin, there was no momentous outcome on the viability of HEK-293 cells. This suggests that the compound, even at concentrations effective against cancer cell lines, did not adversely influence the viability of non-cancerous HEK-293 cells over the specified time periods.

Relative mRNA expression of PARP1 in Apigenin treated HeLa-229 cells

The impact of Apigenin's IC_{50} concentration on the mRNA expression of PARP1 in HeLa229 cells is shown graphically in Figure 5. The outcomes showed that when HeLa-229 cells were treated with Apigenin, the mRNA expression of PARP1 was significantly (p<0.001) lower than in untreated cells. This substantial decrease in PARP1 mRNA expression highlights Apigenin's inhibitory action on PARP1, suggesting that it may be used as a therapeutic drug to target PARP1 in the treatment of cancer.

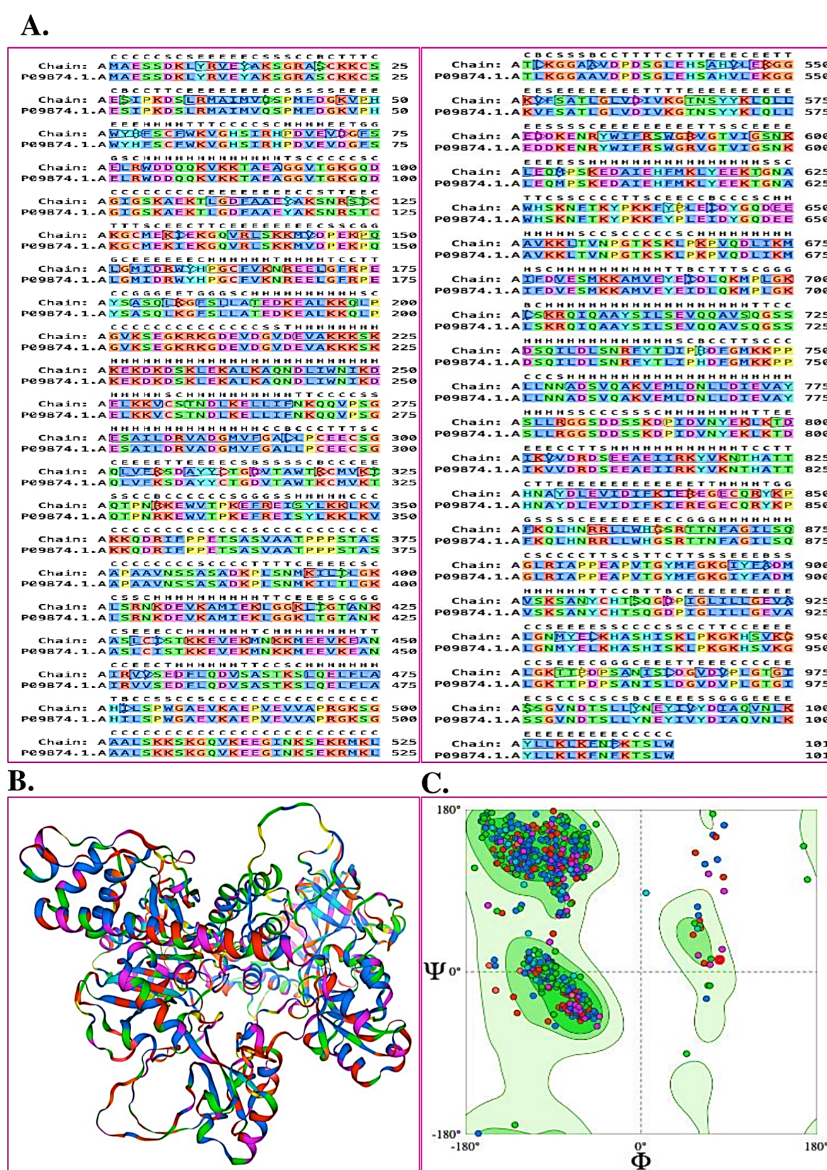

Figure 1: (A) Sequence alignment by template structure. (B) High-resolution PARP1 model from Swiss-MODEL. (C) Ramachandran Plot illustrating energetically favored regions within the protein structure.

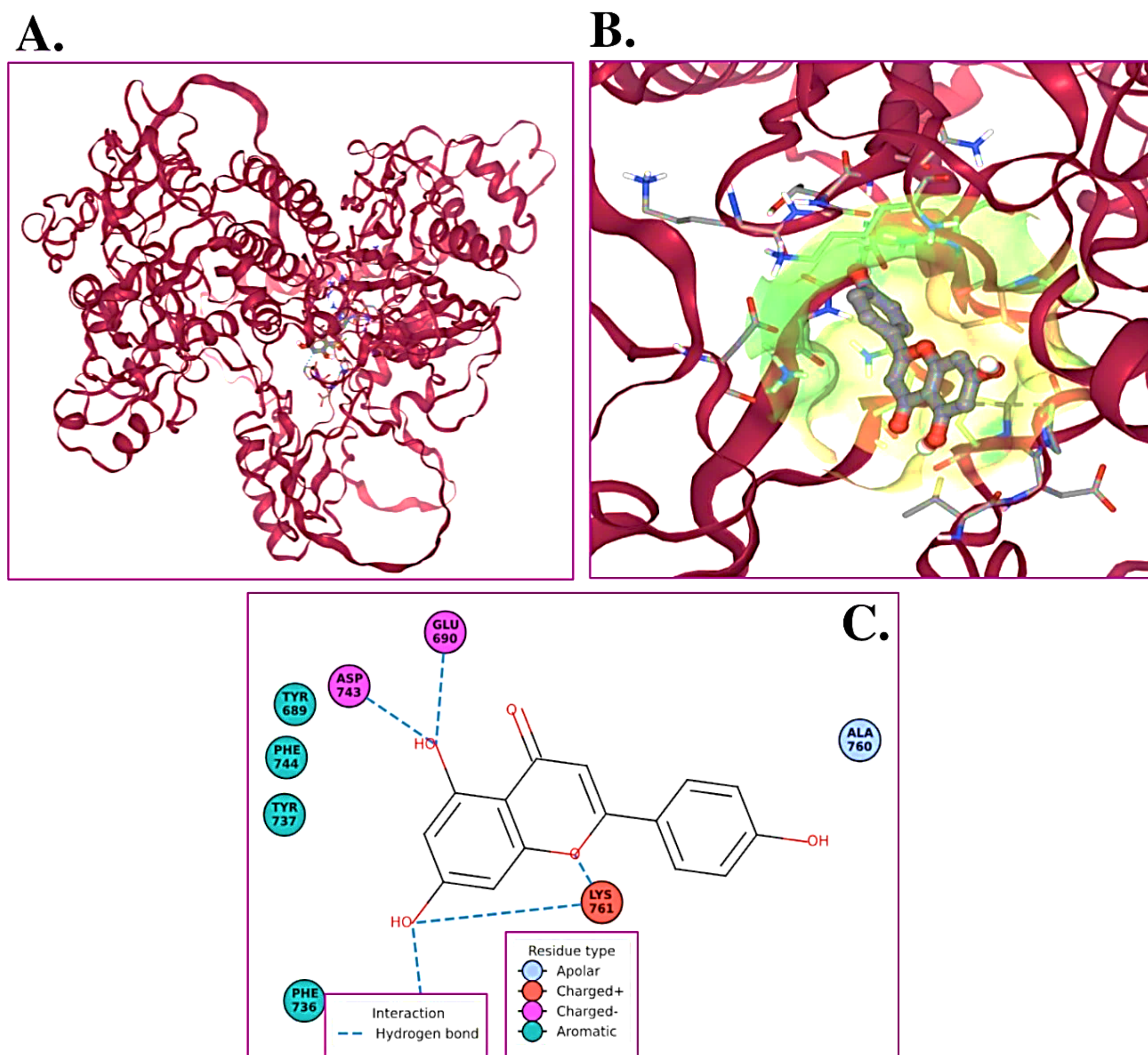

Figure 2: Molecular docking of Apigenin with PARP1. (A) Cartoon presentation of the PARP1: Apigenin complex. (B) Surface view providing additional insights into their interaction. (C) 2D representation of protein-ligand interaction, indicating successful docking and key binding interactions.

DISCUSSION

In gynaecological cancers like ovarian, endometrial, and cervical cancer, where DNA damage repair mechanisms are frequently dysregulated, targeting PARP1 offers a targeted therapeutic approach.[30] By exploiting synthetic lethality, PARP1 inhibitors improve the sensitivity of cancer cells to DNA damage, leading to tumor cell death.[5,28] This targeted therapy holds potential for improved treatment outcomes and reduced toxicity compared to traditional chemotherapy, marking a significant advancement in gynaecological cancer treatment.[7]

The presented findings offer a comprehensive evaluation of the PARP1 model generated via Swiss-MODEL. With a remarkable sequence identity and coverage of 100%, the alignment with the target sequence appears precise. Furthermore, the model's quality assessment, underscores its excellence. Notably, the GMQE score provides an overall measure of model quality, considering alignment coverage.[24] Additionally, the Ramachandran Plot offered valuable insight into energetically favoured regions within the modelled structure.[24] These analyses collectively contribute to a thorough understanding of the model's fidelity and structural integrity, crucial for further research and applications in the field.

The recent advancement in computational techniques has facilitated the identification and exploration of potential therapeutic compounds targeting specific proteins.[25,26,31] The molecular docking analysis suggests a strong binding affinity between Apigenin and PARP1, with evidence of hydrogen bonds and other interactions, indicating a comprehensive binding pattern. The docking results offer profound insights into the interaction between Apigenin and PARP1. Firstly, the calculated binding affinity signifies a robust interaction between the Apigenin and the PARP1, indicating a favourable binding

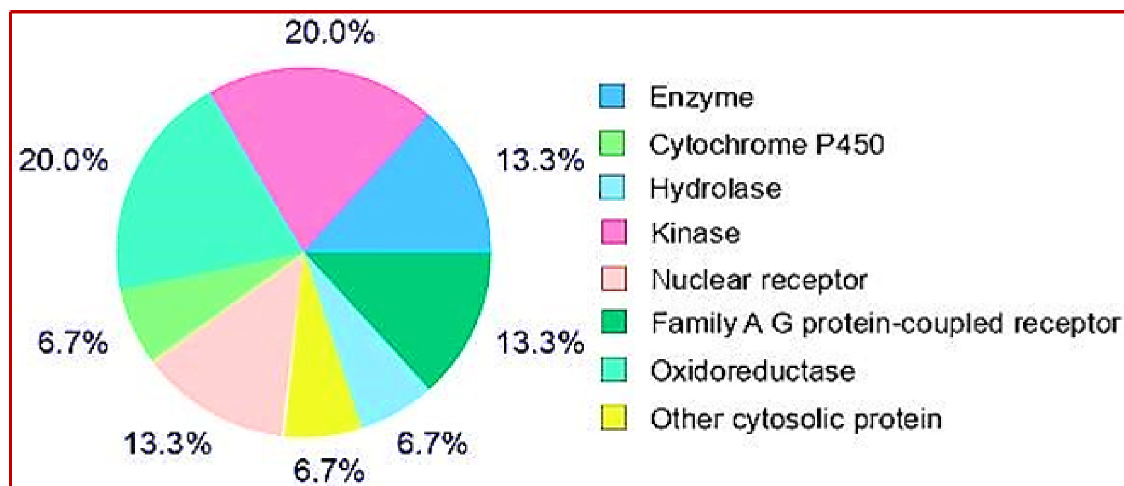

Figure 3: SwissTargetPrediction analysis of Apigenin.

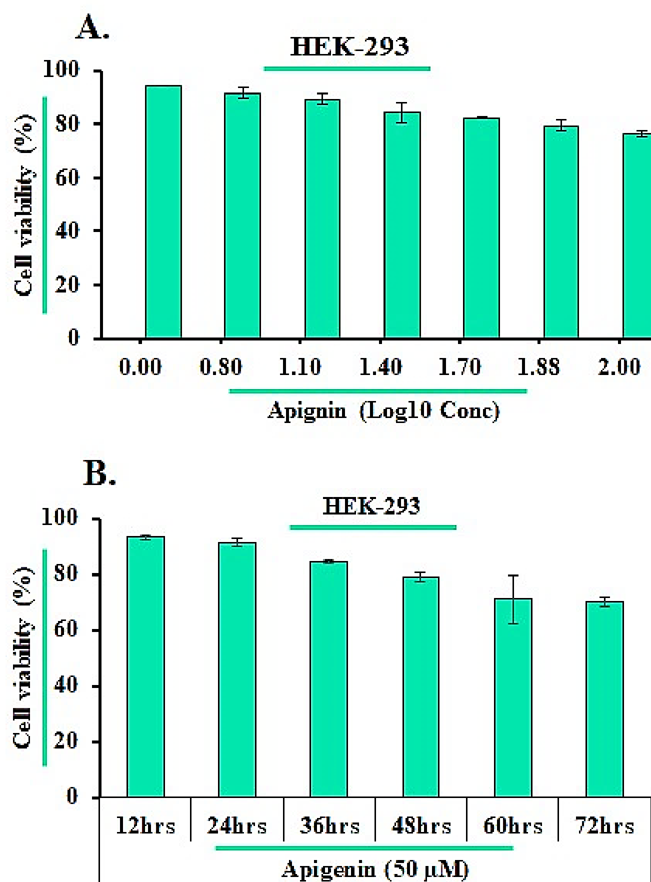

Figure 4: (A) Concentration dependent cytotoxic effect of Apigenin on HEK-293 cells (B) Time-dependent effect of Apigenin on HEK-293 cell viability. HEK-293 cells were treated thru Apigenin for 24, 48, and 72 hr.

configuration. The substantial affinity suggests the potential efficacy of Apigenin as a PARP1 inhibitor. Cartoon presentation of the PARP1: Apigenin complex, offered a spatial understanding of the molecular arrangement. The visualization aided in discerning the specific orientation and positioning of Apigenin within the binding site of PARP1, allowing for a nuanced examination of the interaction interface, thereby enhancing our comprehension of the binding mode. The fruitful docking of Apigenin into the deep binding cavity of PARP1 is evident from the docking pose, indicating a snug fit within the binding pocket. Notably, Apigenin established hydrogen bonds with the ASP743 and GLU690

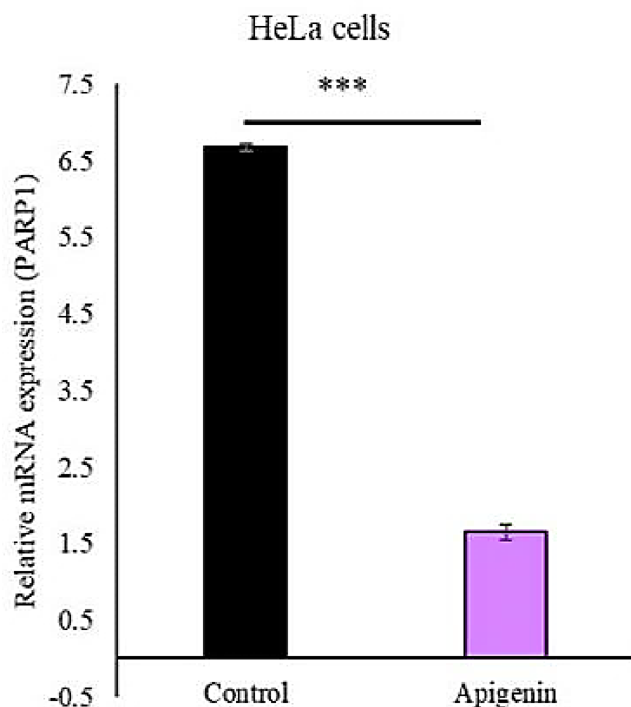

Figure 5: Consequence of Apigenin on PARP1 mRNA Expression in HeLa-229 Cells.

amino acid residues of PARP1, underscoring the specificity of the interaction.

SwissTargetPrediction is a computational tool utilized for the prediction of potential protein targets for small molecules or compounds.[32] This predictive analysis aids in understanding the pharmacological profile and potential therapeutic applications of a given compound by identifying its putative targets within the biological system. The SwissTargetPrediction analysis further highlights the diverse biological activities associated with Apigenin, suggesting its potential therapeutic versatility beyond its interaction with PARP1. This comprehensive analysis strengthens the argument for Apigenin as a promising candidate for further therapeutic exploration.

Cell viability assays provide valuable information about the effects of numerous treatments, such as drugs or compounds, on cell survival, proliferation, and metabolic activity.[33] The results of cell viability assays are crucial for understanding the potential toxicological or therapeutic effects of a substance on different cell types.[34,35] The juxtaposition of findings from cell viability assays and mRNA expression studies provides a comprehensive understanding of Apigenin's potential as a cancer therapeutic agent. While the former suggests a favourable safety profile and selective cytotoxicity towards cancer cells, the latter highlights its specific molecular mechanism of action, particularly in inhibiting PARP1 expression. However, it is essential to warrant the need for further experimentation to elucidate the underlying mechanisms driving the observed effects and to validate the therapeutic relevance of Apigenin *in vivo*.

CONCLUSION

In conclusion, the evaluation presented in this study offers promising insights into the potential of targeting PARP1, particularly in gynaecological cancer treatment. The utilization of computational modelling techniques, such as Swiss-MODEL and molecular docking analysis, has provided a robust foundation for understanding the structural and interactional aspects of the PARP1 protein and its potential inhibitor, Apigenin. The precise alignment and high-quality model generated through Swiss-MODEL underscore the reliability of the PARP1 model, crucial for further investigations and therapeutic applications. Moreover, the molecular docking analysis reveals a strong binding affinity between Apigenin and PARP1, supported by hydrogen bonding interactions, highlighting the potential efficacy of Apigenin as a PARP1 inhibitor. Furthermore, the SwissTargetPrediction analysis elucidates the diverse biological activities associated with Apigenin, suggesting its versatility as a therapeutic agent beyond PARP1 inhibition. The integration of cell viability assays provides critical insights into Apigenin's safety profile and selective cytotoxicity towards cancer cells, complementing the molecular studies. However, additional experimentation is warranted to elucidate the underlying mechanisms and validate Apigenin's therapeutic relevance *in vivo*. Overall, this comprehensive approach enhances our understanding of Apigenin's potential as a promising candidate for further therapeutic exploration in gynaecological cancer treatment.

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ABBREVIATIONS

PDB: Protein Data Bank; **3D:** Three-dimensional; **SDF:** Structure Data files; **MD:** Molecular Docking; **DMSO:** Dimethyl Sulfoxide; **NCCS:** National Center for Cell Sciences; **DMEM:** Dulbecco's Modified Eagle Medium; **FBS:** Fetal Bovine Serum; **qRT-PCR:** Quantitative realtime polymerase chain reaction; **GMQE:** Global Model Quality Estimation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

This study evaluates the potential of targeting PARP1, predominantly in gynaecological cancer treatment, by computational modelling techniques like Swiss-MODEL and

molecular docking analysis. The model's reliability is crucial for further research. The docking analysis reveals strong binding affinity between Apigenin and PARP1, indicating its efficacy. SwissTargetPrediction examination reveals Apigenin's diverse biological activities. Cell viability assays provide insights into Apigenin's safety and cytotoxicity.

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