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Original article

Comparative In Silico Analysis of Wild-Type and Mutant-Type *Akt2* Gene Mutation (C.58c>T) In Type-2 Diabetes Mellitus

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Abstract: Type 2 Diabetes Mellitus (T2DM) is a complex and chronic metabolic disorder that has been frequently linked to single nucleotide polymorphisms (SNPs) in the AKT2 gene. AKT2, a key isoform of the AKT kinase family, plays an essential role in metabolic regulation and has been implicated in the development and progression of several cancers, including ovarian, breast, and pancreatic malignancies. Genetic mutations in AKT2 often lead to impaired insulin signaling and secretion, positioning this gene as a crucial therapeutic target for both metabolic and oncogenic pathologies. In the present study, a computational analysis was undertaken to examine the structural and functional consequences of a specific point mutation in the AKT2 protein. Bioinformatics tools predicted the mutation to be pathogenic, resulting in notable destabilization of the protein's native conformation. To further explore therapeutic interventions, molecular docking simulations were performed with two candidate ligands, MESOBILIVERDIN and MK-2206, against the mutant AKT2 protein. MESOBILIVERDIN exhibited superior binding affinity and enhanced structural stability, with a calculated binding energy of −13.02 kcal/mol, compared to MK-2206, which showed a binding energy of −10.5 kcal/mol. These findings suggest both compounds possess therapeutic potential; however, MESOBILIVERDIN appears to be the more promising ligand for mutation-specific targeting in T2DM.Collectively, this study offers a computational framework for assessing mutation-induced alterations in protein behavior and supports the application of structure-based drug design approaches in the development of targeted therapies for genetically defined subtypes of metabolic disorders.

Keywords: Type 2 Diabetes Mellitus, AKT2 gene, SNPs, insulin signaling, molecular docking, MESOBILIVERDIN, MK-2206, protein stability, pathogenic mutation, structure-based drug design.

Introduction

Metabolic syndrome (MetS) comprises a group of interrelated metabolic disturbances that substantially elevate the likelihood of developing coronary heart disease (CHD), stroke, and type 2 diabetes mellitus (T2DM) [1]. Diabetes mellitus is recognized as a persistent metabolic condition marked by elevated blood glucose levels, which arise due to impaired insulin production, resistance to insulin, or both. This disorder affects approximately 8–9% of the global population. Prolonged hyperglycemia contributes to progressive damage, impaired function, and eventual failure of multiple organs particularly the eyes, kidneys, nerves, cardiovascular system, and blood vessels [2].The three main types of DM include type 1 DM (T1D,insulin-dependent), an autoimmune condition resulting in the destruction of pancreatic β-cells and absolute insulin deficiency; type 2 DM (T2D,non-insulin-dependent), which involves insulin resistance combined with progressive β-cell dysfunction and gestational diabetes mellitus (GDM), a form of diabetes that develops during pregnancy, typically during the second or third trimester. This complex disease is caused by a complex interplay between genetic, epigenetic, and environmental factors, which constitutes over 90% of all diabetes cases globally [3]. With the increasing prevalence and mortality associated with it, it is an emotional and economic burden on the patient and a socioeconomic burden on the country's economy [4]. The prevalence of type 2 diabetes and prediabetes is much higher than previously thought in Pakistan. Comprehensive strategies need to be developed to

incorporate screening, prevention, and treatment of type 2 diabetes at a community level [5]. On a molecular level, insulin signaling pathways play a pivotal role in the maintenance of glucose. One of the critical mediators in this pathway is the AKT2 protein, encoded by the AKT2 gene located on chromosome 19q13.1 [6]. AKT2 is predominantly expressed in insulin-sensitive tissues such as skeletal muscles, liver, and adipose tissue and is essential for mediating insulin's metabolic actions, including glucose uptake and glycogen synthesis [7]. Dysregulation of the PI3K/AKT signaling pathway, in which AKT2 is a key effector, has been strongly associated with the development of insulin resistance, impaired lipid metabolism, and consequently T2D [8]. Mutations and polymorphisms in the AKT2 gene, particularly non-synonymous single-nucleotide polymorphisms (nsSNPs), may result in structural and functional alterations of the AKT2 protein, potentially leading to altered insulin signaling and glucose homeostasis [9]. In the present study Genome Aggregation Database (gnomAD) was utilized to extract genetic variation data specific to the South Asian (SAS) population, to identify highly deleterious missense SNPs of the ATK2 gene via several in silico analyses, that may influence its structure, function, and stability [10]. The integration of genetic variation data with structural modelling and docking analyses provides a powerful platform for identifying critical mutations that could serve as potential biomarkers or drug targets in T2D. These findings may cover the way precision medicine approaches, where individuals at higher genetic risk could be identified early and offered personalized interventions aimed at preventing disease evolution [11]

Materials and Methods

Computational Identification of Potential Targets for Type 2 Diabetes

This study aimed to identify genes associated with Type 2 Diabetes (T2D) by integrating data from multiple bioinformatics databases. Initially, T2D-related genes were retrieved from the MalaCards database (https://www.malacards.org/) in CSV format and from DisGeNET (https://disgenet.com/) in Excel format. To identify common genes between both datasets, gene names were input into Venny 2.1 (https://bioinfogp.cnb.csic.es/tools/venny/), with MalaCards assigned to List1 and DisGeNET to List 2. A Venn diagram was generated to visualize overlaps. In case of no initial overlap, additional gene sets were extracted until shared genes were found. The overlapping genes were then analyzed for functional enrichment and pathway involvement using ShinyGO (https://bioinformatics.sdstate.edu/go/). The gene with the lowest P-value ($P < 0.05$), indicating strong statistical significance, was selected for further analysis. AKT2 emerged as the top candidate due to its strong association with T2D.Further investigation of AKT2 was conducted through the OMIM database (https://www.omim.org/), confirming its relevance to disease pathology and mutation-related dysfunction. Finally, structural analysis was performed using bioinformatics tools to examine potential 3D conformational changes in the protein, offering deeper insight into its role in T2D pathogenesis.

Dataset Retrieval

Single nucleotide polymorphisms (SNPs) within the human AKT2 gene were obtained from the Genome Aggregation Database (gnomAD) (https://gnomad.broadinstitute.org/), a comprehensive resource that compiles extensive data on human genetic variation, including SNPs and insertion-deletion polymorphisms. This database supports diverse applications in genetic and functional research. For this study, SNP data specific to the South Asian (SAS) population were extracted from gnomAD. One of the key variants identified was gnomAD ID: 19-40233814-G-T.

Variant Analysis via Mutation Taster

To assess the pathogenicity of the selected gene variant, MutationTaster (https://www.mutationtaster.org/) was used. The specific mutation analyzed was a C replaced by T substitution at position 58 with "T" selected as the mutated base. The tool provided results for both the wild and mutant sequences, indicating the potential impact of the mutation.

Predicting the Pathogenic

Effects of nsSNPs (mutation)

For the analysis of the pathogenic nature of SNPs, several software algorithms are available. The analysis of potential effects of SNPs involved the utilization of Functional Analysis through Hidden Markov Models (FAThMM), [q1] Sorting Intolerant from Tolerant (SIFT) Sequence, and Polymorphism Phenotyping (poly-Phen2) were used to identify the nsSNPs that can be further directed to downstream analysis. These examinations classify the impact as

either tolerable or damaging. FATHMM (Functional analysis through Hidden Markov Models) (https://fathmm.biocompute.org.uk/) . In FATHMM FASTA format, information about the amino acid sequence along with its ENSEMBL transcript ID is given to the server for predicting the impact of single-nucleotide variants (SNVs), which yields highly accurate predictions for SNVs across the entire human genome. SIFT(https://sift.bii.a-star.edu.sg/) predicts that single-nucleotide substitutions in the amino acid sequence are higher probability to disrupt protein function. In polyphen-2 (http://genetics.bwh.harvard.edu/pph2/) , the FASTA format information of the amino acid sequence along with its position and substitution is given to the server, which classifies the input, indicating a neutral effect or negative effect. All these servers show "NO SEQUENCE RECORD FOUND" which is indication of Pathogenic nature of the SNPs mutation.

Predicting the Impact of SNPs on Protein Stability

Protein strength can be regulated by single-nucleotide polymorphisms (SNPs), which can either reduce or enhance protein stability. The tools I-Mutant and Mupro can be used to predict these effects. I-Mutant (https://folding.biofold.org/i-mutant/i-mutant2.0.html) is utilized to predict the effect of mutation (SNPs /SNV) on the protein stability. Mupro (https://mupro.proteomics.ics.uci.edu/) algorithm is also used to detect alterations in protein stability and protein state due to mutation or variation (SNV) in the amino acid sequence. I-Mutant classifies the input mutation effect on protein stability, which gives further direction towards finding protein structure. Mupro predicts that the selected mutated Variant (SNV) is correct, which indicates the protein is nonfunctional and not stable. If the selected protein shows instability, then we further proceed towards finding the protein structure.

Predicting Structures

In AlphaFold3 (https:alphafoldserver.com/), the FASTA format amino acid sequence of wild and mutant type protein is given, which gives correct structure of protein. From PDB (https://www.rcsb.org/), MESOBILIVERDIN (Natural ligan) and MK-2206 (synthetic ligand) ligands for the desired gene is obtained, then the final structure for that ligand comes from PubChem.

Docking of Ligand with Target Proteins

Molecular docking was performed using AutoDock Vina (v1.5.7),was used for the prediction and design of new probable drugs via possible docking modes, and the binding affinity between the PDB structure of the target protein and the ligand molecule was analyzed. Protein structure (WT and MT) was generated via AlphaFold 3 (https://alphafoldserver.com/) . Ligand for target protein is obtained from PDB, and structure is downloaded from pub chem, converted into PDB format using PyMol. For docking

1-Prepare the protein and ligand structure

For preparation, protein is uploaded in Autodock tool and remove hydrogen bonds and add polar water molecules and charges then save in PDBQT format. For ligand the PDB form is loaded into Autodock and after preparation save in PDBQT format. 2-Select the docking site/ Grid in protein After preparation both structures are uploaded in PDBQT format and select docking site in protein structure by creating grid dimensions (Grid site have pocket regions for docking),which is saved in config file. 3-Carry Out Protein-Ligand docking Using Docking Tool. For Docking, AutoDock Vina is run via Command Prompt. Through codes, files name is instructed which contain structures (protein, ligand in PDBQT format),Vina tools and in response run docking. Each docking run produced a binding energy (ΔG) score in kcal/mol. Lower ΔG values indicated stronger binding affinity, which is shown in Reports and in Results. In these studies, were use 2 different ligands for docking for T2D.

Visualization of complex

The docking poses and molecular interactions were analyzed using the PLIP tool (https://plip-tool.biotec.tu-dresden.de/plip-web/plip/index). The docked complexes were examined to emphasize the crucial binding features, such as hydrogen bonding, hydrophobic contacts, and electrostatic interactions between the ligand and the target gene.

Normal Mode Analysis Using IMOD

In place of traditional molecular dynamics simulations, Normal Mode Analysis (NMA) was utilized to investigate the flexibility and dynamic behavior of protein–ligand complexes. The analysis was performed through the IMOD server (https://imods.iqf.csic.es/), which models macromolecules as elastic networks to assess their intrinsic motions. The wild-type (WT) and mutant (MT) protein–ligand complexes were subjected to NMA to evaluate how structural

flexibility is influenced by specific mutations. Changes in deformation energy and residue mobility were analyzed to determine the mechanical effects introduced by the mutations, potentially affecting the functional behavior of the protein.

RESULTS

Identification of Type 2 Diabetes (T2D)-Associated Genes

A systematic investigation of Parkinson's disease–related genes was conducted using data retrieved from the MalaCards and DisGeNET databases. Overlapping gene candidates were identified through comparative analysis with the Venny 2.1 tool. These shared genes were subsequently analyzed for functional enrichment using ShinyGO, which identified several significantly enriched pathways associated with Diabetes disease. Among the intersecting genes, AKT2 emerged as the most strongly associated candidate, exhibiting the lowest p-value ($P < 0.05$), thereby underscoring its potential involvement in the disease's molecular pathology. The key candidate genes were further analyzed for mutation types and functional impacts. Protein sequences in FASTA format were retrieved from the Protein Data Bank (PDB). The specific sequence under investigation is detailed in Table 1

Table 1: protein sequence used in the current study

Protein information	AKT2
Ensemble transcript ID	ENST00000392038
Protein sequence	MNEVSVIKEGWLHKRGEYIKTWRPRYFLLKSDGSFIGYKERPEAPDQTLPLNNFSVAEC-QLMKTEPRNTFVICLQWTTVIERTFHVSPDEREEWMRAQMVANSLKQRAPGEDPMDYK CGSPSDSSTTEEMEVAVSKRAVTMNDFDYLKLLGKGTFGKVILVREKATGRYYAMKIL-RKEVIIADEVAHTVTESRVLQNTRHPFLTALKYAFQDRLCFVMEYANGGELFHLSRERVF TEERARFYGAEIVSALEYLHSRDVVYRDKLENLLDKDGHIKITDFGLCKEGISDGATMKTF CGTPEYLPEVLEDNGRADWWGLGVVMYEMMGRPFYNQDHFLIEIRPRTLSPEAKSLLAG LLKKDPKQRLGGGSDAKVMEHRFFLSIWQDVVQKKLPPFKPQTSETRYFDDEFTAQSITID RYDSLG LLELDQRTHF PQFSYSASIRE

Pathogenicity Prediction of nsSNPs mutation

The selected non-synonymous SNP (nsSNP) in the AKT2 gene were evaluated using 3 computational tools:

FATHMM

Mutated sequence of protein using proper Ensemble ID is given to server which indicates the pathogenic nature of mutation by obtaining FATMM score of -1.63.

- FATHMM SCORE > 0.5 (Pathogenic, Damaging).
- FATHMM SCORE ≤ 0.5 (Benign, Tolerated).

SIFT

The evaluated mutation C>T received a SIFT score of <.05 , suggesting that it is likely to be deleterious which indicates its pathogenicity.

- SHIFT VALUE ≤0.05 = Deleterious (pathogenic)
- SHIFT VALUE >0.05 = Tolerated (benign)

PolyPhen-2

PolyPhen-2 also failed to classify the mutation by showing "NO SEQUENCE RECORD FOUND", supporting its pathogenic effect.

Stability Impact of the Mutation

The impact of the SNP mutation on AKT2 protein stability was evaluated using I-Mutant 2.0 and Mupro. Both tools predicted a decrease in stability. I-Mutant showed a negative $\Delta\Delta G$ value, indicating a destabilizing effect, while Mupro confirmed the mutation as destabilizing, suggesting impaired folding and potential loss of function.

Interpretation of Ramachandran outliers

The Ramachandran plot is a graphical representation used in structural biology to visualize the allowed and disallowed dihedral angles ϕ (phi) and ψ (psi) of amino acids residues in a protein structure. Before performing molecular docking, the stereochemical integrity of both wild-type and mutant AKT2 protein structures was assessed through Ramachandran plot analysis. The wild-type structure showed 3.34% (16 residues) in disallowed regions, whereas the mutant exhibited a slightly higher value of 4.23% (21 residues). Although both fall within the acceptable threshold (<5%), the elevated outlier percentage in the mutant suggests subtle alterations in backbone conformation, which may influence the protein's structural stability and ligand-binding capacity. These findings underscore the importance of conducting further docking and stability analyses.

Ramachandran outliers of Mutant tyoe

The mutant protein structure exhibits notable deviations in its backbone geometry, as reflected by the Ramachandran plot analysis. A total of 21 residues (4.23%) is identified as Ramachandran outliers, which significantly exceeds the acceptable threshold of <0.05%. This high percentage of outliers suggests that several residues in the mutant model adopt energetically unfavorable conformations, indicating potential issues with model accuracy or local steric strain. Additionally, only 86.49% of residues fall within the favored regions, falling short of the ideal >98% goal. These results suggest that the mutant structure may suffer from conformational instability or poor stereochemical quality in certain regions. Despite these concerns, the Ramachandran distribution Z-score of -1.44 ± 0.36 remains within the acceptable range (|Z|<2), suggesting that the overall distribution is still statistically reasonable, albeit less ideal than desired.

Table 2: Protein Geometry -Mutant Type

Parameter	Value	Percentage	Goal
Poor rotamers	5	1.12%	<0.3%
Favored rotamers	433	97.30%	>98%
Ramachandran outliers	21	4.23%	<0.05%
Ramachandran favored	429	86.49%	>98%
Rama distribution Z-score	-1.44 ± 0.36	–	abs(Z score) < 2
MolProbity score	2.27	61st percentile	–
Cβ deviations > 0.25 Å	0	0.00%	0
Bad bonds	1 / 4183	0.02%	0%
Bad angles	8 / 5648	0.14%	<0.1%

Ramachandran outliers of Wild Type

In contrast, the wild type of protein structure shows relatively better, though still imperfect, backbone geometry. A total of 16 residues (3.34%) is classified as Ramachandran outliers lower than in the mutant model but still well above the recommended limit of <0.05%. This indicates that while the wild type of structure performs slightly better in terms of backbone torsion angles, it too requires further refinement. Importantly, 92.07% of residues are in the favored regions, a higher value than that of the mutant but still below the optimal threshold. The Ramachandran Z-score of -0.79 ± 0.36 is within the acceptable range and closer to zero than the mutant's, reflecting a more balanced and statistically sound φ/ψ angle distribution. Overall, the wild type of structure demonstrates improved geometry over the mutant, though both models show room for structural improvement.

Table 3: Protein Geometry -Wild Type

Parameter	Value	Percentage	Goal
Poor rotamers	3	0.70%	<0.3%
Favored rotamers	416	97.20%	>98%
Ramachandran outliers	16	3.34%	<0.05%
Ramachandran favored	441	92.07%	>98%
Rama distribution Z-score	-0.79 ± 0.36	–	abs(Z score) < 2
MolProbity score	1.90	81st percentile	–
Cβ deviations > 0.25 Å	2	0.44%	0
Bad bonds	0 / 4019	0.00%	0%
Bad angles	17 / 5429	0.31%	<0.1%

Protein–Protein Interaction (PPI) Network Analysis of AKT2

To investigate the functional relationships of the AKT2 protein before proceeding with molecular docking, a protein–protein interaction (PPI) network was generated using the STRING database (https://string-db.org/). The resulting network identified strong associations between AKT2 and several critical signaling proteins, such as AKT1, GSK3B, FOXO1, FOXO3, PIK3CA, and PHLPP1. These interactions indicate that AKT2 plays a central role in regulating key biological processes, including insulin signaling, glucose metabolism, and cell survival. The analysis underscores AKT2's importance as a regulatory hub, thereby justifying its selection for downstream docking studies and mutation impact assessment.

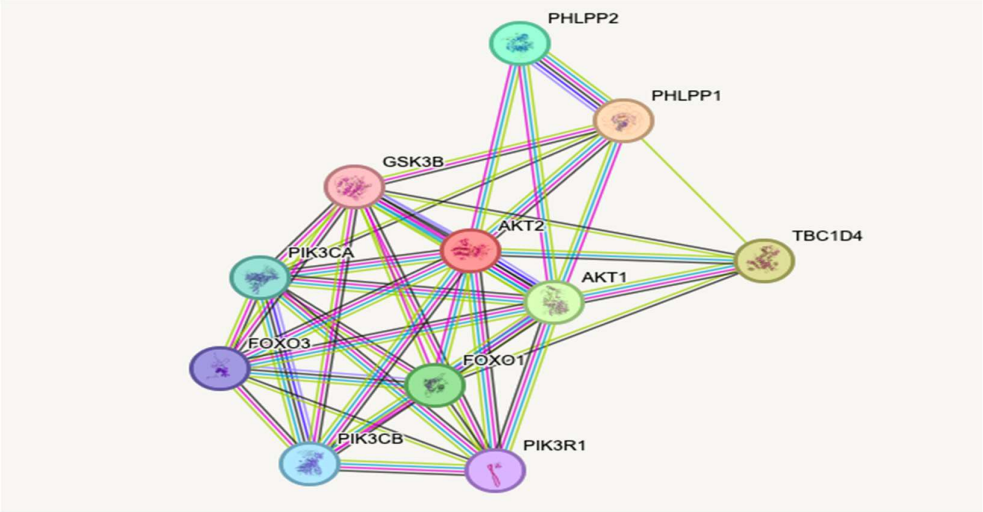

Figure-1: The protein–protein interaction (PPI) network of AKT2 was generated using the STRING database, where the thickness of the connecting lines represents the confidence level or strength of evidence supporting each interaction.

Table-3. Protein –protein network stats by STRING analysis

Protein-protein network stats	AKT2
number of nodes	11
number of edges	40
average node degree	7.27
avg. local clustering coefficient	0.86
expected number of edges	17
PPI enrichment p-value	2.8e-06

Molecular Docking

To investigate protein–ligand interactions, molecular docking was performed using AutoDock Vina. The docking results of Meso-Biliverdin (Natural Ligand) and MK-2206 (Synthetic ligand) with the AKT2 protein revealed distinct binding affinities and conformational variations, as reflected by their differing binding energy scores which are shown in table 4.

Table 4: Docking analysis of AKT2 with Meso-Biliverdin and MK-2206

Ligand	Protein	Binding Energies (Kcal/Mol)
MESO BILIVERDIN	Wild	-12.52
	Mutant	-13.02
MK-2206	Wild	-10.09
	Mutant	-10.5

Analysis Of Dock Complex

Comparative analysis of Dock complex revealed that the Mesobiliverdin show stronger binding with mutant protein with the binding affinity of -13.02kcal/mol) as compared to wild type (-12.52kcal/mol),driven by 2 salt bridges (ASP ,ASP) and expanding hydrophobic contacts indicating compatibility with mutant protein, these expanding residues play a crucial role in stabilizing the ligand binding within the active site of mutant protein through a combination of hydrophobic, polar, and charged interactions, same for MK-2206 (synthetic ligand) which also show stronger binding of (-10.5 kcal/mol) with mutant protein as compared to wild protein with binding interaction (-10.09 kcal/mol). If we compare analysis of docked results revealed that the MESO BILIVERDIN (natural ligand0 had the binding affinity of (-13.02 kcal/mol) and MK-2206 (synthetic ligand) had the binding affinity of (-10.5 kcal/mol). Thus, Mesobiliverdin (natural ligand) had the more binding affinity with AKT2 protein. Molecular docking analysis between AKT2 and the ligands revealed key stabilizing interactions at the binding site. These interactions suggest that Mesobiliverdin and MK-2206 both ligands hold potential as a therapeutic candidate for targeting the mutant AKT2 protein, making it a promising scaffold for future drug design and inhibitor screening efforts.

Table 4: Binding Interactions in MUT_PROTEIN (Ligand: UNK-Z:0 – alpha-aminobutyric acid)

Type	Index	Residue	AA	Distance (Å)	Additional Info
Hydrophobic	1	82A	THR	3.43	Ligand Atom: 4132, Protein Atom: 685
	2	275A	ASP	3.73	Ligand Atom: 4101, Protein Atom: 2253
Hydrogen Bond	1	86A	ARG	2.39 (H-A), 3.10 (D-A)	Donor Angle: 128.7°, Protein Donor: ✓, Side Chain: ✓, Donor Atom: 721 [Ng+], Acceptor Atom: 4110 [O3]
	2	274A	ARG	2.10 (H-A), 3.07 (D-A)	Donor Angle: 167.6°, Protein Donor: ✓, Side Chain: ✓, Donor Atom: 2247 [Ng+], Acceptor Atom: 4111 [O3]
	3	274A	ARG	2.31 (H-A), 2.91 (D-A)	Donor Angle: 165.1°, Protein Donor: ✗, Side Chain: ✓, Donor Atom: 4135 [O3], Acceptor Atom: 2241 [O2]
	4	277A	LYS	3.19 (H-A), 3.85 (D-A)	Donor Angle: 123.5°, Protein Donor: ✓, Side Chain: ✓, Donor Atom: 2273 [Nζ+], Acceptor Atom: 4127 [O3]
	5	296A	LEU	3.47 (H-A), 3.81 (D-A)	Donor Angle: 103.1°, Protein Donor: ✗, Side Chain: ✗, Donor Atom: 2417 [Nam], Acceptor Atom: 4127 [O3]
Salt Bridge	1	275A	ASP	4.19	Protein Positive: ✗, Ligand Group: Quart amine, Ligand Atom: 4115
	2	275A	ASP	3.58	Protein Positive: ✗, Ligand Group: Tetramine, Ligand Atom: 4122

Normal Mode Analysis

Normal Mode Analysis (NMA) performed using the iMOD server indicated that the Mesobiliverdin–AKT2 complex exhibited lower RMSD values, suggesting enhanced structural stability and tighter ligand–protein interactions. In contrast, the MK-2206–AKT2 complex demonstrated higher RMSD (B-factors) and increased deformability, indicating greater structural fluctuations and reduced stability of the interaction.

Table 4. Summary of hydrophobic, hydrogen bond, and salt bridge interactions between MUT_PROTEIN and alpha-aminobutyric acid (UNK-Z:0) as identified by PLIP.

Features	MK-2206	Mesobiliverdin ligand
Deformability Peaks	Higher and more frequent	Lower and fewer
B-factor (NMA & PDB)	Higher and broader	Lower, more consistent
RMSD / Flexibility	More fluctuation	Less fluctuation
Binding Stability (Interpretation)	Less stable	More stable

Discussion

This computational analysis highlights the significant role of AKT2 as a key molecular regulator in the pathophysiology of Type 2 Diabetes Mellitus (T2DM), particularly within the South Asian population, which is genetically diverse and predisposed to metabolic disorders. Through integrated bioinformatics tools, a deleterious non-synonymous SNP was identified in the AKT2 gene. Pathogenicity prediction tools FATHMM, SIFT, and PolyPhen-2-collectively supported the damaging nature of the variant, suggesting impaired protein function. Structural stability assessments via I-Mutant and Mupro revealed a notable reduction in protein stability, further supported by Ramachandran plot analysis, where the mutant model displayed an increased percentage of outliers, indicating conformational changes in the backbone geometry. Such alterations may affect the structural integrity of the protein and its binding efficiency. The STRING-based protein–protein interaction (PPI) network emphasized AKT2's central role within the PI3K/AKT signaling pathway, interacting with key metabolic regulators including PIK3CA, FOXO1, GSK3B, and PHLPP1. These interactions underline AKT2's involvement in insulin signaling, glucose uptake, and cell survival processes. Molecular docking simulations provided comparative insights into the binding profiles of two ligands—MESOBILIVERDIN (natural) and MK-2206 (synthetic)-with both wild-type and mutant forms of AKT2. MESOBILIVERDIN exhibited higher binding affinity (−13.02 kcal/mol with the mutant protein) compared to MK-2206 (−10.5 kcal/mol), owing to its ability to form salt bridges, electrostatic interactions, and extended hydrophobic contacts. These results indicate that MESOBILIVERDIN may be more structurally compatible with the mutated AKT2 conformation. To investigate the dynamic properties of ligand-protein complexes, Normal Mode Analysis (NMA) was performed. The MESOBILIVERDIN–AKT2 complex demonstrated lower RMSD values and minimal B-factor fluctuations, signifying greater conformational stability. In contrast, the MK-2206 complex showed higher flexibility and deformability, suggesting a weaker and less stable interaction. Collectively, these results suggest that MESOBILIVERDIN holds potential as a mutation-specific therapeutic agent for T2DM. The study also demonstrates the effectiveness of an in silico integrative approach—combining SNP analysis, structural modeling, molecular docking, and flexibility dynamics—for identifying and characterizing potential drug candidates. Such computational frameworks can guide future precision medicine strategies, enabling targeted interventions for individuals with genetic predispositions to metabolic diseases like T2DM.Future experimental studies, including in vitro binding assays and in vivo efficacy testing, are essential to validate MESOBILIVERDIN's therapeutic potential and assess its pharmacokinetic and safety profiles.

Conclusion

This study highlights the pathogenic impact of a specific nsSNP in the AKT2 gene, which plays a crucial role in glucose metabolism, insulin signaling, and cancer progression. Two ligands, MESOBILIVERDIN and MK-2206, were evaluated for their binding potential with mutant AKT2 using molecular docking and normal mode analysis. MESOBILIVERDIN showed superior binding affinity (−13.02 kcal/mol) and enhanced structural stability, making it a stronger candidate than MK-2206.The mutant AKT2 structure showed reduced conformational integrity, suggesting its role in T2DM pathology. These findings support MESOBILIVERDIN as a promising therapeutic lead for mutation-specific T2DM treatment. Further experimental studies (in vitro/in vivo) are needed to validate and translate these computational insights into clinical application.

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