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Investigating the Therapeutic Potential of Vildagliptin: Molecular docking of Diabetic Targets IL-1β, PI3K, and AS160

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Abstract

Diabetes mellitus is a complex metabolic disorder characterized by impaired glucose homeostasis and chronic inflammation. In recent years, the role of various molecular targets in the pathogenesis of diabetes has gained significant attention. This study aimed to explore the potential therapeutic effects of Vildagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, against key diabetic targets including interleukin-1 β (IL-1 β), phosphoinositide 3-kinase (PI3K), and Akt substrate of 160 kDa (AS160). IL-1 β is a pro-inflammatory cytokine known to contribute to the development of insulin resistance and pancreatic β-cell dysfunction. Experimental evidence suggests that Vildagliptin may exert an inhibitory effect on IL-1β production and signaling, thereby attenuating inflammation in diabetes. The PI3K/Akt pathway plays a crucial role in glucose metabolism and insulin signaling. Impaired PI3K signaling has been implicated in insulin resistance, a hallmark of type 2 diabetes. Studies have demonstrated that Vildagliptin treatment can enhance PI3K activity, leading to improved insulin sensitivity and glucose uptake in peripheral tissues. AS160, an Akt substrate, regulates glucose transport by modulating the translocation of glucose transporter 4 (GLUT4) to the plasma membrane. Reduced AS160 phosphorylation has been observed in insulin-resistant states. Vildagliptin has been reported to enhance AS160 phosphorylation, promoting GLUT4 translocation and enhancing glucose uptake in skeletal muscle and adipose tissue. This study comprehensively examines the effects of Vildagliptin on IL-1β, PI3K, and AS160 in the context of diabetes using molecular docking.

Keywords: Diabetes mellitus, Vildagliptin, molecular docking, PI3K, glucose metabolism, therapeutic development.

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Introduction

Type 2 diabetes mellitus is a multifactorial disease influenced by a combination of genetic predisposition and lifestyle factors. It is characterized by insulin resistance, where the body's cells become less responsive to insulin, and inadequate insulin secretion from the pancreas [1]. Management of type 2 diabetes typically involves a comprehensive approach that includes lifestyle modifications, oral antidiabetic medications, and, in some cases, insulin therapy. In recent years, there has been a growing focus on developing novel chemotherapies for diabetes that target the underlying mechanisms of the disease and aim to enhance glucose regulation [2]. These emerging therapies seek to address specific pathways involved in insulin production, insulin signaling, glucose metabolism, and immune system modulation [3]. Researchers are exploring the potential of novel medications that specifically target these pathways.

By developing drugs that act on key molecular targets, such as enzymes and receptors involved in insulin production and signaling, scientists aim to improve the body's ability to regulate blood glucose levels [4]. Advancements in insulin therapy have also played a significant role in diabetes management. The development of insulin analogues with improved pharmacokinetic and pharmacodynamic profiles has allowed for more precise control over blood glucose levels. These analogues come in various forms, including rapid-acting, long-acting, and ultra-long-acting insulin analogues [5]. They offer increased convenience and reduced risk of hypoglycaemia compared to traditional insulin formulations. Furthermore, the field of gene therapy and regenerative medicine holds promise for future diabetes treatments. Research efforts are underway to develop gene and cell therapies that aim to restore normal insulin production and function by introducing functional genes or cells into the body [6].

Vildagliptin is an oral antidiabetic medication that belongs to the class of dipeptidyl peptidase-4 (DPP-4) inhibitors. It is primarily used in the management of type 2 diabetes mellitus [7]. Vildagliptin works by inhibiting the enzyme DPP-4, which is responsible for the rapid degradation of incretin hormones. When we consume food, incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released from the intestines [8]. These hormones stimulate the release of insulin from pancreatic beta cells and inhibit the release of glucagon from pancreatic alpha cells, resulting in enhanced glucose-dependent insulin secretion and reduced glucose production by the liver. Vildagliptin works by inhibiting DPP-4, thereby prolonging the action of GLP-1 and GIP. This leads to increased insulin secretion, decreased glucagon secretion, and improved regulation of blood glucose levels [9].

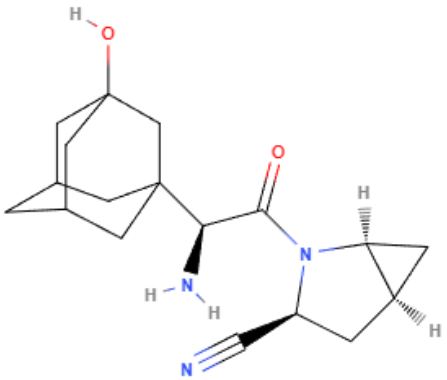

Fig 1. Structure of Vildagliptin

Molecular docking is a computational technique extensively employed in structure-based drug design, allowing the analysis of the interaction between a smaller molecule and a larger macromolecule [10]. It assesses the complementary fit and spatial docking at specific binding sites. In our study, we utilized molecular docking to investigate the molecular mechanisms of vildagliptin,

a compound used in the treatment of diabetes, concerning its interaction with diabetic regulators, specifically IL-1β, PI3K, and AS160.

Materials and methods:

Protein preparation:

In order to conduct our molecular docking studies, we obtained the crystal structures of the diabetic regulating targets, namely IL-1β, PI3K, and AS160 from the Protein Data Bank (PDB) using the respective PDB IDs: IL-1 β (1ILB), PI3K (5XBJ), and AS160 (3QYB). We specifically focused on Chain A of each protein structure, as it represented the primary protein of interest in our analysis. To prepare these protein structures for molecular docking simulations, we employed a Python molecule viewer. This software allowed us to remove water ions and ligands, ensuring that only the protein component remained for further analysis. This step was crucial for streamlining the docking process and focusing solely on the protein-drug interactions.

Ligand preparation:

In this study, we selected vildagliptin (CID ID: 6918537) as our compound of interest. The three-dimensional (3D) structure of vildagliptin was obtained from PubChem, a comprehensive database of chemical molecules. To evaluate the drug-like properties of vildagliptin, we utilized the SWISS-ADME prediction tools. These tools provided valuable insights into various drug-related properties, including solubility, lipophilicity, and drug-likeness, aiding in the assessment of its potential as a therapeutic compound. The refined structures and calculated partial charges were saved as mol2 files, which were subsequently processed using AutoDock Tools (ADT) to generate pdbqt files. Pdbqt files are a necessary format for conducting molecular docking studies using AutoDock, a widely used software for performing molecular docking simulations. To optimize the geometry and minimize the energy of the synthetic compounds, we employed the Avogadro server. This process involved refining the 3D coordinates of the compounds, including vildagliptin. Through this optimization, we enhanced the geometry of the synthetic drug, ensuring a more accurate representation of its structure. Additionally, we calculated the partial charges of vildagliptin to account for its electrostatic properties.

Molecular docking procedure:

For the docking analysis, we employed AutoDock, a widely used software for molecular docking simulations [11]. To define the active site regions within IL-1β, PI3K, and AS160, grid maps were generated using AutoDock. The dimensions of the grids were set to a box size of 90 × 90 × 90 xyz points, with the center aligned to the active site residues.The dock scores and conformers of the compounds bound to the SBD of IL-1β, PI3K, and AS160 were calculated and evaluated using AutoDock. This allowed us to assess the binding affinities and potential interactions of the compounds with the target proteins.To generate the necessary grid maps, we utilized AutoGrid, a component of the AutoDock software suite. The grid maps provided a spatial representation of the active site regions, enabling accurate docking simulations within the specified regions of interest. This algorithm allows for the rotation of all torsions during the docking process. Additionally, the pseudo-Solis and Wets methods were applied for minimization, using default parameters. The active site residues in the substrate-binding domain of IL-1β, PI3K, and AS160 were determined using Discovery Studio 4.5.

Results:

In our study, our objective was to explore the regulatory activity of diabetic regulators, namely IL-1β, PI3K, and AS160, by investigating their interactions with vildagliptin through molecular

docking analysis. Specifically, we focused on examining the molecular interactions between the diabetic treating compound vildagliptin and the active sites of IL-1β, PI3K, and AS160 proteins. To effectively identify compounds that could strongly bind to the DNA binding domain of the targeted proteins, we utilized the crystal structures of the diabetic regulatory proteins as the basis for our study. Before proceeding with the molecular docking simulations, we carefully analyzed the binding sites within the IL-1β, PI3K, and AS160 proteins. To facilitate this process, we employed the receptor grid generation panel, which allowed us to generate a grid map for each receptor. In this step, a scaling factor of 1.0 was applied to ensure accurate mapping of the binding site. For the docking simulations, we employed a docking protocol that enabled us to explore all reasonable orientations of each low-energy conformer within the designated binding site. During the docking process, the torsional degrees of freedom of the ligand (vildagliptin) were relaxed, while the conformation of the protein remained fixed. This approach allowed us to evaluate the potential binding modes and interactions between vildagliptinand the targeted proteins. Overall, our study utilized the crystal structures of the targeted proteins to investigate compounds capable of effectively binding to the DNA binding domain. We generated receptor grid maps and performed docking simulations using a specific docking protocol. By considering various orientations and relaxing the torsional degrees of freedom of the ligand, while keeping the protein conformation fixed, we aimed to gain insights into the molecular interactions between vildagliptin and the diabetic regulatory proteins.

The results obtained from our molecular docking analysis, as summarized in Table 1, provided insights into the binding affinities of vildagliptin with the diabetic regulating targets, namely IL-1β, PI3K, and AS160. In comparison, vildagliptin exhibited higher binding energies with the diabetic targets, with values of -6.9 kcal/mol for IL-1β, -8.0 kcal/mol for PI3K, and -6.5 kcal/mol for AS160. These binding energies indicate the strength of the interactions between vildagliptin and the target proteins. The 3D structural representations of the docking analysis, as depicted in Figure 2, visually illustrated the formation of hydrogen bonds between vildagliptin and specific active site residues within the diabetic regulating targets. Notably, interactions occurred at residues GLN79 for IL-1β, VAL851 for PI3K, and SER1082 for AS160. These hydrogen bonds play a crucial role in stabilizing the binding of vildagliptin to the target proteins and further emphasize the potential interactions between the compound and the active sites. The significant binding affinities observed suggest that vildagliptin has the capability to inhibit inflammatory activity through its interaction with the diabetic regulating targets. This indicates that vildagliptin, as a diabetic drug, holds promise as a lead compound for targeting the signaling pathways involved in diabetes. By interacting with IL-1β, PI3K, and AS160, vildagliptin has the potential to offer an improved therapeutic outcome in the treatment of diabetes.

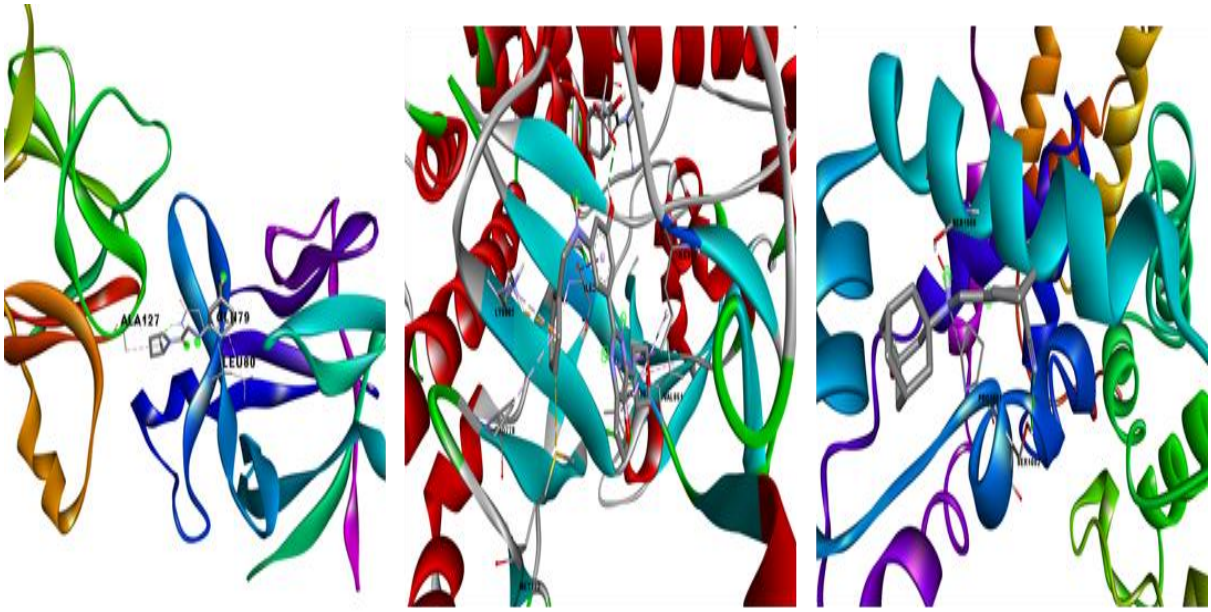

Fig 2.Molecular docking analysis of vildagliptin with diabetic regulating targets (IL-1β (left), PI3K (*middle*), and AS160 (right).

Table 1. Molecular docking analysis

S. no	Drug	Protein	Binding energy (kcal/mol)	No. of H bonds involved	Amino acid residues
1.	Vildagliptin (6918537)	IL-1β	-6.9	1	Gln79
2.		PI3K	-8.0	1	Val851
3.		AS160	-6.5	1	Ser1082

Conclusion:

In this study, our objective was to investigate the interaction between the diabetic drug Vildagliptin and key regulatory proteins involved in diabetic-mediated disorders, namely IL-1β, PI3K, and AS160. These proteins are known to play crucial roles in the regulation of diabetic pathways. Through molecular docking analysis, we explored the binding affinities between vildagliptin and these diabetic targets. The results of our docking analysis revealed significant associations in terms of binding affinities between vildagliptin and the diabetic regulatory proteins, IL-1β, PI3K, and AS160. This indicates that vildagliptin has the potential to interact and modulate the activity of these proteins, thereby influencing the diabetic-mediated processes.

Conflict of interests:

No conflict of interest from any of the authors.

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