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Computational Drug Repurposing Study Identifies Rimegepant as a Promising DPP4 Inhibitor for Type 2 Diabetes

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Abstract: Type 2 diabetes mellitus (T2D) is a chronic metabolic disorder characterized by insulin resistance and impaired glucose regulation, with Dipeptidyl Peptidase 4 (DPP4) being a key therapeutic target. This study aimed to identify potential DPP4 inhibitors among the screened compounds from the approved drug library using curcumin as a matrix through the in-silico approaches. Ligand-based virtual screening (LBVS) was performed using DrugRep software, leading to the identification of ten (10) compounds from the approved drug library. Subsequently, structure-based virtual screening (SBVS), including molecular docking, was conducted to evaluate the binding affinity of these compounds to the DPP4 enzyme. The screened compounds exhibited binding affinities ranging from -7.0 to -9.9 kcal/mol, while the reference compound Sitagliptin showed a binding affinity of -8.3 kcal/mol within the active site of the DPP4 enzyme. Rimegepant emerged as the most promising candidate, exhibiting stronger binding affinity for key residues such as Pro510, Leu514, and Arg560 compared to the reference drug, Sitagliptin, which interacted with Val585, Thr565, Pro475, Gly576, and Arg560. Furthermore, network pharmacology analysis was conducted to investigate the mechanism of action of Rimegepant in modulating key pathways associated with T2D, including DPP4 inhibition, which influences the insulin resistance signaling pathway. Moreover, the physicochemical and pharmacokinetic profiles indicate that Rimegepant possesses favorable drug-like properties. These findings indicate that Rimegepant may have potential as a therapeutic candidate for T2D; however, the study is limited to in-silico analyses. Further molecular dynamics (MD) simulations and experimental validation, including in vitro and in vivo studies, are necessary to confirm its efficacy and safety before any clinical application.

Keywords: anti-diabetic; DPP4; ligand-based virtual screening; structure-based virtual screening; molecular docking; network pharmacology.

1. Introduction

Diabetes is a long-term metabolic disorder characterized by chronic hyperglycemia resulting from impaired insulin secretion, insulin action, or both. Its global prevalence continues to rise at an alarming rate, posing substantial burdens on healthcare systems, economies, and communities [1]. According to the International Diabetes Federation (IDF), approximately 463 million adults were living with diabetes in 2019, and this figure is expected

to escalate to 700 million by 2045. The disease is associated with severe complications, including cardiovascular disorders, nephropathy, neuropathy, retinopathy, and heightened susceptibility to infections, all of which substantially increase morbidity and mortality [2]. Although insulin therapy and oral hypoglycemic agents remain the cornerstones of treatment, these interventions are often limited by side effects, reduced efficacy over time, and the risk of treatment resistance. Consequently, there is a growing demand for safer and more effective therapeutic options for long-term glycemic management [3].

In recent years, intensified research efforts have focused on identifying new therapeutic agents to address the multifaceted nature of Type 2 Diabetes (T2D). Natural products have received significant attention for their potential efficacy, broad pharmacological properties, and comparatively lower adverse effects [4]. Among them, *Curcuma longa* (*C. longa*) has emerged as a particularly promising source of bioactive compounds for diabetes management. Curcumin, the principal active component of *C. longa*, has demonstrated notable anti-diabetic and anti-inflammatory properties [5]. Clinical studies report that curcumin can significantly reduce fasting blood glucose (MD = –11.48 mg/dL) and HbA1c levels (MD = –0.54%), along with decreasing circulating inflammatory markers such as C-reactive protein [6, 7]. Improvements in insulin sensitivity have been attributed to its ability to modulate adiponectin and leptin levels, enhance antioxidant defense mechanisms, and improve lipid homeostasis [8, 9]. Furthermore, advanced formulations such as nano-curcumin have been developed to overcome its limited bioavailability, although further studies are needed to determine optimal dosing and duration for clinical use [10, 11]. These findings support the potential of curcumin as a complementary therapy; however, its role underscores the broader need to discover more potent, targeted, and clinically viable anti-diabetic agents [6-8].

Among the molecular targets explored in modern anti-diabetic drug discovery, dipeptidyl peptidase 4 (DPP4) has gained considerable prominence due to its pivotal role in glucose metabolism. DPP4 is a serine protease responsible for degrading incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are essential regulators of postprandial insulin secretion and glycemic balance [12, 13]. Inhibition of DPP4 preserves endogenous incretin levels, thereby prolonging insulin secretion, reducing glucagon release, and improving overall glucose homeostasis. Clinically available DPP4 inhibitors, collectively known as gliptins, have demonstrated significant reductions in HbA1c, improved fasting and postprandial glucose levels, and minimal risks of weight gain or hypoglycemia [14-16]. Their additional benefits in enhancing β-cell function and reducing systemic inflammation further highlight DPP4 as a valuable target in T2D management [17, 18].

Despite these advancements, the need for novel DPP4 inhibitors remains critical, particularly in the context of drug resistance, long-term safety concerns, and variability in patient response. Drug repurposing offers a compelling strategy to accelerate the discovery of new therapeutic agents by identifying alternative uses for approved drugs with established safety profiles. This approach can significantly reduce the time, cost, and risk associated with traditional drug development pathways.

The present study aims to identify potential DPP4 inhibitors for T2D through computational drug repurposing strategies. Using an approved drug library, ligand-based virtual screening (LBVS) was first employed to shortlist candidate molecules, followed by structure-based virtual screening (SBVS) through molecular docking to determine the most promising lead compound. Network pharmacology analysis was then conducted to elucidate

the potential mechanisms of action of the identified lead against T2D. The overall workflow for targeting the DPP4 enzyme with selected compounds is illustrated in Figure 1.

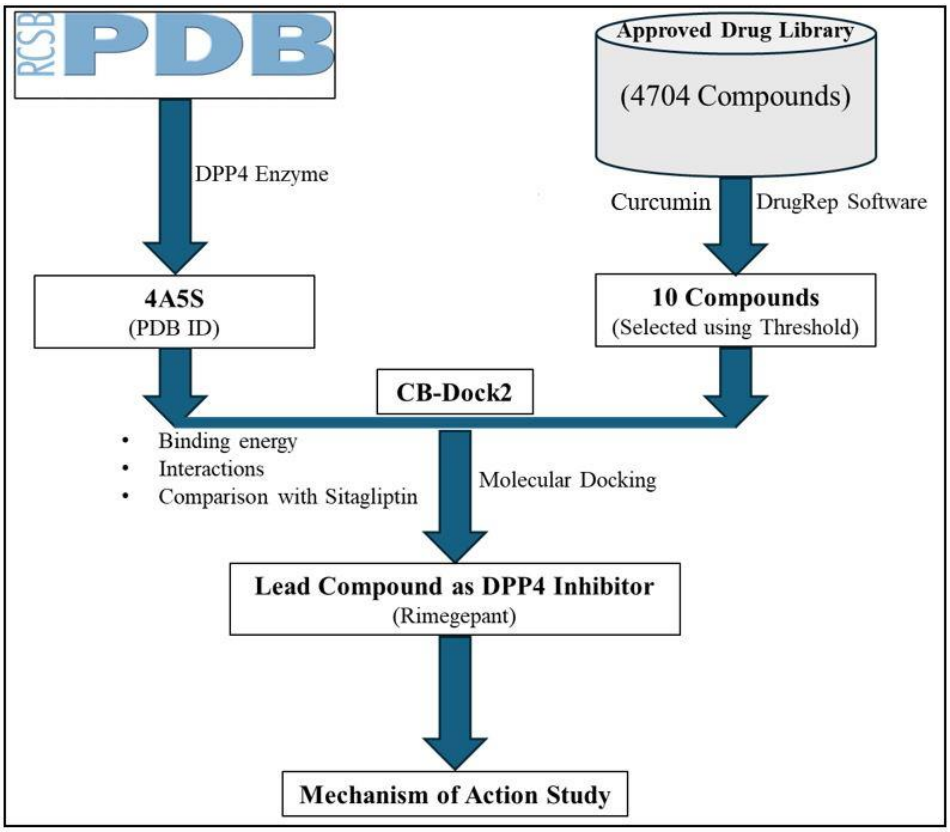

Figure 1. Design strategy for selected compounds targeting the DPP4 enzyme.

2. Materials and Methods

2.1. Query ligand selection.

Curcumin is a major compound of Turmeric (*C. longa*) showing anti-diabetic activity [19, 20]. Based on the anti-diabetic activity, curcumin was selected as the matrix or user compound.

2.2. Ligand-based virtual screening.

The curcumin structure was constructed in ChemSketch and saved in .mol format to perform LBVS of the approved drug library using the DrugRep software [21]. The saved file was imported into the DrugRep software, the threshold was set to 10 to retrieve the top ten compounds, and the analysis was executed. The software then generated the results.

2.3. Structure-based virtual screening.

The selected ten compounds were designed using ChemSketch software and saved in .mol format for molecular docking analysis. Additionally, the crystal structure of human DPP4, with a resolution of 1.62 Å, was obtained from the literature [22] and downloaded from the RCSB Protein Data Bank under the PDB ID 4A5S [23]. Prior to docking, 1599 water molecules and 333 heteroatoms were removed from the protein structure. The Cavity Detection Blind Docking 2 (CB-Dock2) approach was employed to perform rigid docking of curcumin and its analogs into the target protein's active site [24]. This technique utilizes AutoDock Vina for molecular docking, automatically identifying binding sites, determining the center and

dimensions, and adjusting the docking box size based on the query ligands [25]. Several prominent binding cavities were selected for further investigation, and molecular docking was performed at each site. The docking results were analyzed by comparing the binding positions with the co-crystal ligand binding site, and the docking scores were evaluated against the reference compound, Sitagliptin, to identify the most promising lead compound for further study.

2.4. Mechanism of action of Rimegepant against T2D.

The SMILES representation of Rimegepant was retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). Genes associated with T2D were gathered by searching the GeneCards database (https://www.genecards.org/) using the keyword "Diabetes type 2." Additionally, genes linked to Rimegepant were obtained from the SwissTargetPrediction (http://www.swisstargetprediction.ch/) and SuperPred (https://prediction.charite.de/index.php) databases. The overlapping genes between T2D-related and Rimegepant-associated genes were identified using Venny 2.1.0 (https://bioinfogp.cnb.csic.es/tools/venny/). A target interaction network between Rimegepant and T2D was then created using the STRING database (https://string-db.org/cgi/input.pl) and visualized with Cytoscape 3.10.2 software.

To explore the genomic relationship between Rimegepant and T2D, Gene Ontology (GO) enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses were conducted using the DAVID database (https://davidbioinformatics.nih.gov/summary.jsp). The findings were visualized through microinformatics online tools (https://www.bioinformatics.com.cn/). GO enrichment analysis identified three key functional components: Molecular Function (MF), Cellular Component (CC), and Biological Process (BP). For further analysis and visualization, the top 10 enriched terms in each category with a p-value < 0.01 were selected. Additionally, KEGG pathway analysis was used to examine the molecular pathways linking Rimegepant to T2D based on the overlapping gene set.

2.5. Physicochemical and pharmacokinetic properties.

The ADME (absorption, distribution, metabolism, and excretion) properties of Rimegepant were predicted using the SwissADME web tool (http://www.swissadme.ch) [26]. Molecular structure was submitted in SMILES format, and physicochemical and Pharmacokinetic descriptors were calculated using the built-in predictive models.

3. Results and Discussion

3.1. Query ligand selection and ligand-based virtual screening.

Curcumin (Figure 2) has shown considerable promise as an anti-diabetic agent by targeting DPP4. Molecular docking studies indicate that curcumin binds strongly to DPP4, inhibiting its enzymatic activity and preventing the breakdown of GLP-1, thereby enhancing insulin secretion and regulating blood glucose levels [27, 28]. In vitro studies demonstrate that curcumin effectively reduces DPP4 activity in Caco-2 cells and inhibits ERK phosphorylation in muscle cells, outperforming synthetic inhibitors such as DPP4i [27]. These findings are further supported by animal studies, where curcumin administration significantly lowers fasting blood glucose, improves glucose tolerance, and reduces HbA1c levels in diet-induced

diabetic mice [27, 28]. Clinical trials in patients with T2DM further validate curcumin's therapeutic potential, as supplementation leads to decreased HbA1c, fasting serum insulin, and inflammatory markers, highlighting its role as an adjunct treatment [8]. Furthermore, clinical trials also indicate that curcumin supplementation (e.g., 1,500 mg/day for 12 months) significantly reduces fasting blood glucose and HbA1c, improves β-cell function (higher HOMA-β), and lowers insulin resistance (HOMA-IR) as well as body weight in T2D patients [29, 30]. Meta-analyses of randomized controlled trials further support these findings, demonstrating consistent reductions in glycemic indices and HOMA-IR with curcumin therapy [31]. Mechanistically, curcumin exerts its effects by activating the AMPK and PI3K/Akt pathways, enhancing GLUT4-mediated glucose uptake, reducing inflammation (e.g., via NF-κB inhibition), and modulating gut microbiota to improve insulin sensitivity [32-34]. Moreover, curcumin analogs exhibit even stronger binding affinity to DPP4 (-7.6 to -7.7 kcal/mol) compared to the clinically used inhibitor saxagliptin (-6.9 kcal/mol), suggesting the potential for more effective derivative compounds [35].

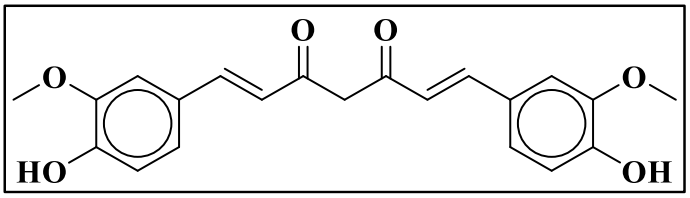

Figure 2. Curcumin was used to screen the DrugBank database.

Compounds for this investigation were selected from an approved drug library using ligand-based virtual screening (LBVS) via the DrugRep online service. DrugRep is an online platform integrated with three libraries: Traditional Chinese Medicine (TCM), Experimental Drugs, and Approved Drugs [21]. A total of 4,704 compounds were screened using DrugRep, leading to the identification of 10 compounds based on a predefined similarity threshold (Figure 3 and Table S1). The similarity and ranking scores of these selected compounds ranged from 0.861 to 1.000. The threshold value (similarity score ≥ 0.86) was selected based on the distribution of the similarity scores generated during the LBVS. Compounds scoring ≥0.86 represented the upper range of structural similarity to the query molecule, ensuring a stringent cut-off for identifying the most relevant candidates. This threshold allowed us to consistently narrow the list to the top ten compounds with the highest predicted similarity, thereby maintaining both specificity and meaningful chemical relevance in the selection process.

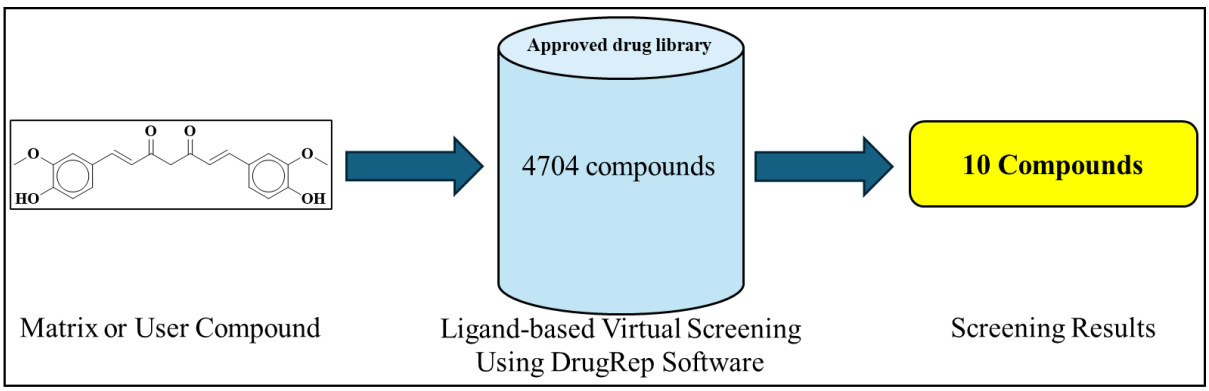

Figure 3. The procedure of the LBVS method.

3.2. Structure-based virtual screening.

SBVS is a powerful computational approach that is essential for efficient, cost-effective lead optimization. This method focuses on understanding the three-dimensional molecular structure of a biological target [36]. SBVS predicts the interaction between a protein and a ligand by employing docking techniques and scoring functions to estimate the free binding energy of the complex while exploring its conformational space [37]. The success of SBVS largely depends on the quality of both the protein structure and the ligand library. Notably, this approach does not require the physical existence of the molecules, as various free software tools and online platforms are available for conducting these simulations.

In this study, similarity scores generated by the DrugRep software were used to identify potential compounds, which were subsequently molecularly docked against the human DPP4 enzyme using the CB-Dock2 program. CB-Dock is a blind docking approach that autonomously detects binding sites, determines the center and dimensions, adjusts the docking box size based on the query ligands, and performs molecular docking using AutoDock Vina. This method enhances docking efficiency and accuracy by predicting target protein binding sites through a curvature-based cavity detection approach (CurPocket) and determining ligand binding poses using AutoDock Vina. Additionally, grid coordinates were adjusted individually for each ligand to optimize the docking process.

Compared to the reference compound sitagliptin, most of the tested compounds successfully docked at the DPP4 enzyme's binding site, demonstrating lower interaction energies, hydrogen bonding, and hydrophobic interactions (Table 1). The selected compounds exhibited binding energies ranging from -7.0 to -9.8 kcal/mol, whereas Sitagliptin displayed a binding energy of -8.3 kcal/mol. Among them, Rimegepant showed a binding energy of -9.3 kcal/mol and formed three hydrogen bonds with Pro510, Leu514, and Arg560 residues. Additionally, it established a carbon-hydrogen bond with Phe559 and a halogen bond with Val558. Strong alkyl and pi-alkyl interactions were also observed with Pro475, Pro510, Lys512, and Ile529 residues (Figure 4a). Furthermore, the hydrogen bond residues Pro510, Leu514, and Arg560, which we observed in our docking model, are located in the vicinity of DPP4's structural framework and may contribute to ligand stabilization, possibly through hydrophobic and electrostatic interactions. In contrast, Sitagliptin formed two hydrogen bonds with Val585 and Thr565, along with three carbon-hydrogen or pi-donor hydrogen bonds involving Pro475, Gly576, and Arg560. It also interacted with other residues, including Pro510 and Asn562 (halogen: fluorine), Ile529 (pi-sigma), Phe559 (pi-pi T-shaped), as well as Leu477, Leu504, Met509, and Lys512 through alkyl and pi-alkyl interactions (Figure 4b).

Table 1. Docking score of selected compounds and the reference (Sitagliptin) compound onto the active site of DPP4 enzyme (PDB ID: 4A5S).

Compound name	Vina score (Kcal/mol)	Interactions
Sitagliptin (Reference compound)	-8.3	Val585, Thr565 (H), Pro475, Gly576, Arg560 (C-H/pi-D H), Pro510, Asn562 (Halogen: Fluorine), Ile529 (pi-sigma), Phe559 (pi-pi T-shaped), Leu477, Leu504, Met509, Lys512 (alkyl/pi-alkyl)
Curcumin	-7.7	Asp501, Asn562, Thr565 (H), Ser511 (C-H), Ile529 (pi-sigma), Leu477, Leu504, Lys512, Ile529, Arg560 (alkyl/pi-alkyl)
Rimegepant	-9.3	Pro510, Leu514, Arg560 (H), Phe559 (C-H), Val558 (Halogen: Fluorine), Pro475, Pro510, Lys512, Ile529 (alkyl/pi-alkyl)
Vinflunine	-8.2	Pro475 (H), Asp501 (C-H)
Rifampicin	-9.8	Asp501 (C-H)
Benazepril	-8.0	Met509 (H), Ser511 (C-H), Leu477, Leu504, Pro475, Pro510, Lys512, Ile529 (alkyl/pi-alkyl)

Compound name	Vina score (Kcal/mol)	Interactions
Vindesine	-7.5	Asp501 (H), Glu452 (C-H), Pro475, Lys512, Leu514 (pi-alkyl)
Vilanterol	-7.0	Arg40, Pro475, Arg560 (H), Leu504 (C-H), Pro510, Lys512, Phe559, Leu477, His533, Pro532 (alkyl/pi-alkyl)
Rifapentine	-8.1	Pro475 (H), Pro532 (C-H)

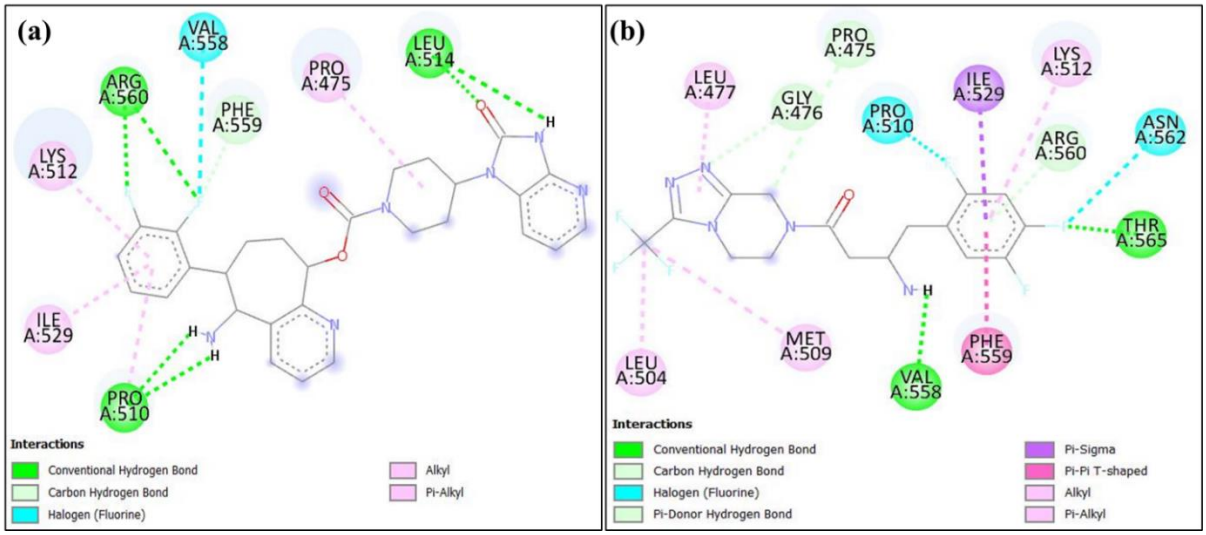

Figure 4. Molecular docking of **(a)** Rimegepant; **(b)** the reference compound (Sitagliptin) onto the active site of DPP4 (PDB ID: 4A5S).

Pro510 and Leu514 are integral components of the hydrophobic S2 pocket, playing a crucial role in the enzyme's substrate specificity by stabilizing interactions with the hydrophobic regions of inhibitors. Arg560, situated near the catalytic site, forms hydrogen bonds with acidic functional groups of inhibitors, thereby enhancing binding affinity and selectivity. While cyanopyrrolidine-based inhibitors such as Sitagliptin are known to interact with residues like Glu205, Glu206, and Tyr662, Pro510 and Leu514 contribute to shaping the S2 pocket's structure, indirectly influencing inhibitor positioning [13]. Additionally, Arg560's electrostatic interactions provide further stability to inhibitor-enzyme complexes, as observed in structural studies of DPP4 inhibitors, where charged residues near the active site enhance binding efficiency [38, 39]. These key residues collectively impact the enzyme's conformational dynamics and inhibitor effectiveness, making them essential targets for rational drug design to improve potency and reduce off-target effects. Based on binding energy and interactions with these critical residues, Rimegepant demonstrated the strongest inhibition of DPP4 among the selected compounds and the reference drug sitagliptin. Therefore, due to its highest binding affinity and superior interactions with key amino acid residues compared to Sitagliptin, Rimegepant was identified as the lead compound.

3.3. Mechanism of action of rimegepant against T2D.

A comprehensive dataset of 18760 T2D-associated targets was obtained from the GeneCards database, all of which were unique genes (Table S2). Additionally, 254 potential targets related to Rimegepant were identified through the SwissTargetPrediction (Table S3) and SuperPred (Table S4) databases, among which 245 were unique (Table S5). The intersection analysis between the 18760 T2D-associated targets and the 245 Rimegepant-related targets identified 232 common targets (Figure 5 and Table S6). Although target prediction analysis initially identified 254 potential targets for Rimegepant, of which 245 were unique, only 7 targets appear as Rimegepant-specific in the Venn diagram. This is because the

Venn diagram represents only those targets that remain after dataset harmonization, gene-name standardization, and confidence-based filtering. Many of the initially predicted targets were removed during the curation process because they were duplicates, non-standard identifiers, low-confidence predictions, or lacked validated gene annotations in the T2D-related dataset. After applying these filtering steps, only 7 high-confidence targets were exclusive to Rimegepant, while 232 targets overlapped with T2D-associated genes. Therefore, the small number of Rimegepant-only targets in the Venn diagram reflects a refined, high-quality subset that meets strict inclusion criteria, rather than the absence of additional predicted interactions.

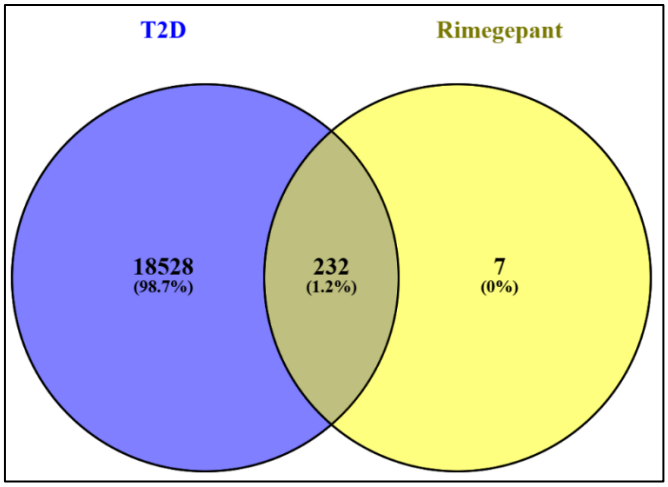

Figure 5. Venn diagram of the core target at the intersection of Rimegepant-related targets and T2D-related targets.

A protein-protein interaction (PPI) network was built using the STRING database based on the 232 common target genes to clarify the possible molecular processes of Rimegepant (Table S7). To identify linkages between nodes, an interaction score threshold of >0.485 was used, and isolated targets were eliminated (Figure 6a). The final network had an average degree value of 15.7 and consisted of 1820 edges and 232 coupled nodes. Software called Cytoscape 3.10.2 was used to visualise the PPI network (Figure 6b). Additionally, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses were conducted for the 232 overlapping genes using DAVID software.

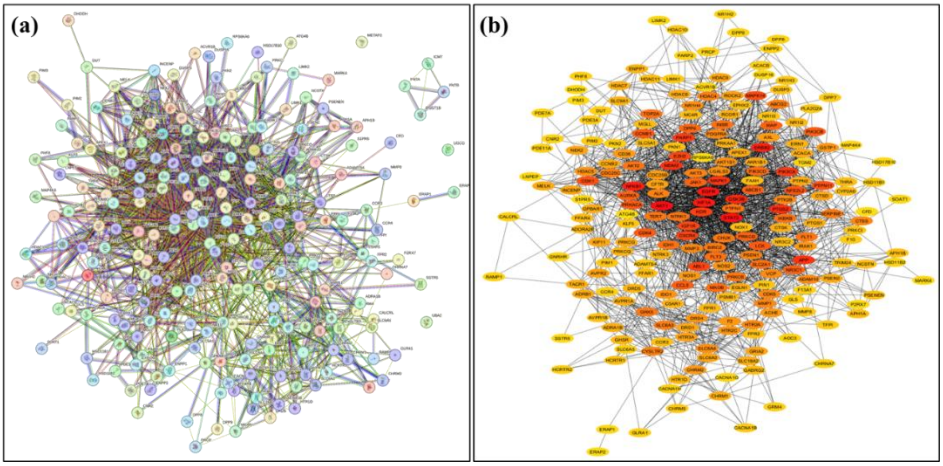

Figure 6. PPI plot of key targets of Rimegepant-related targets and T2D-related targets. **(a)** PPI plot using SRING Software; **(b)** PPI plot using Cytoscape 3.10.2 software.

The 232 common target genes were subjected to GO enrichment and KEGG pathway analysis better to understand the molecular processes of Rimegepant in lung cancer. The DAVID database was used for the functional annotation, which divided GO words into three main categories: Biological Process (BP), Cellular Component (CC), and Molecular Function (MF) (Tables S8, S9, and S10). The top 10 items in each category (p-value < 0.01) were carefully visualised from the 544 BP-related phrases, 100 CC-related terms, and 214 MF-related terms found by the GO analysis.

Protein phosphorylation, chromatin remodeling, protein autophosphorylation, insulin receptor signaling pathway, inflammatory response, insulin-like growth factor receptor signaling pathway, platelet-derived growth factor receptor-beta signaling pathway, chemical synaptic transmission, epidermal growth factor receptor signaling pathway, and negative regulation of apoptotic process were the most enriched pathways in the BP category. The plasma membrane, cytoplasm, receptor complex, dendrite, synapse, gamma-secretase complex, neuron projection, cytosol, presynaptic membrane, and postsynapse were the most frequently identified target proteins for CC. The most important functional characteristics in the MF category were the following: ATP binding, protein serine kinase activity, protein kinase activity, protein serine/threonine kinase activity, histone H2AXY142 kinase activity, histone H3Y41 kinase activity, histone H3T6 kinase activity, histone H3T11 kinase activity, AMP-activated protein kinase activity, and transmembrane receptor protein tyrosine kinase activity.

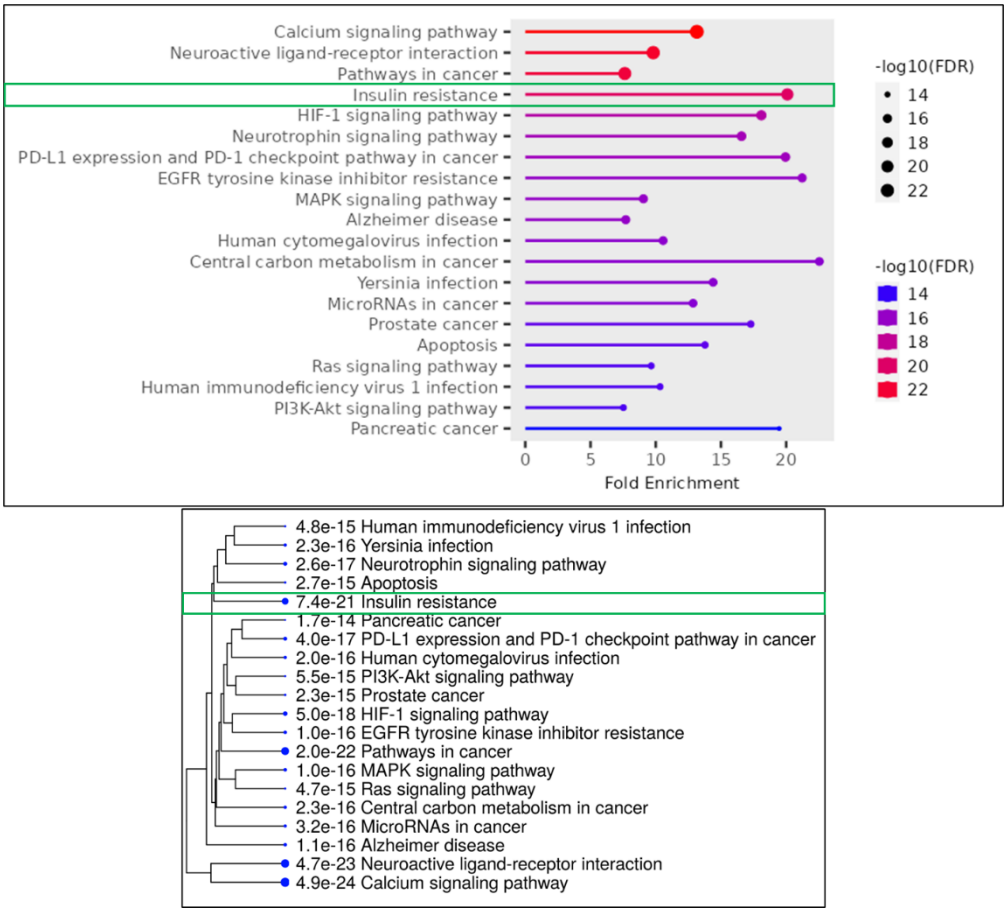

Figure 7. KEGG pathway enrichment analysis of Rimegepant-related targets and T2D-related targets. The green box represents the plausible signalling pathway for the treatment of Rimegepant against T2D.

Furthermore, the top 20 pathways (p-value < 0.01) were visualised by KEGG pathway enrichment analysis (Table S11). The Calcium signaling pathway, Insulin resistance,

Neuroactive ligand-receptor interaction, HIF-1 signaling pathway, PD-L1 expression and PD-1 checkpoint pathway in cancer, Pathways in cancer, EGFR tyrosine kinase inhibitor resistance, Neurotrophin signaling pathway, Central carbon metabolism in cancer, MAPK signalling pathway, Alzheimer disease, Human cytomegalovirus infection, Yersinia infection, MicroRNAs in cancer, Prostate cancer, Apoptosis, Ras siganalling pathway, Human immunodeficiency virus 1 infection, PI3K-Aktsiganniling pathway and pancreatic cancer were the most significantly enriched (Figure 7).

Insulin interacts with its receptor, triggering the activation of tyrosine kinase, which subsequently phosphorylates insulin receptor substrates (IRS). These phosphorylated IRS proteins then recruit downstream signaling molecules such as PI3K and Akt. The PI3K/Akt pathway is essential for glucose metabolism, facilitating GLUT4 translocation to the plasma membrane for glucose uptake while suppressing hepatic gluconeogenesis. However, disruptions in this pathway, caused by chronic inflammation, oxidative stress, or serine phosphorylation of IRS proteins, impair insulin signaling and contribute to insulin resistance [40, 41].

Additionally, insulin signaling intersects with other regulatory pathways, including AMPK and mTOR. AMPK activation enhances glucose uptake and fatty acid oxidation, whereas mTOR plays a role in protein synthesis but can also interfere with insulin signaling through feedback inhibition [42]. Systems biology research has identified key genetic networks, such as MAPK and FOXO, that are implicated in the progression of T2DM and serve as potential therapeutic targets [42, 43]. Understanding these molecular mechanisms has driven the development of novel treatments, including GLP-1 receptor agonists and SGLT2 inhibitors, which modulate these pathways to enhance glycemic control [42, 44].

3.3. Physicochemical and pharmacokinetic properties.

ADME studies are critical in drug discovery because they provide essential insight into how a potential therapeutic behaves in the body and help predict its pharmacokinetic fate. Poor ADME profiles are a leading cause of drug candidate failure, often due to insufficient absorption, rapid clearance, or toxic metabolites, which makes early screening of these properties a cost-effective strategy [45]. By integrating in silico, in vitro, and in vivo ADME assessments early in the drug development pipeline, researchers can identify and de-risk molecules that may have suboptimal pharmacokinetics or safety liabilities [46, 47]. Moreover, applying ADME profiling during lead optimization enhances the efficiency of the discovery process by focusing on compounds with favorable pharmacokinetic properties, ultimately reducing attrition rates in later phases [48, 49].

The ADME evaluation of Rimegepant was performed using the SwissADME platform, and the results are summarized in Table 2. Rimegepant has a molecular weight of 534.56 g/mol, which slightly exceeds the recommended upper limit of 500 g/mol; however, most other physicochemical parameters remain within the acceptable ranges for orally active compounds. The molecule possesses eight hydrogen bond acceptors (HBA) and two hydrogen bond donors (HBD), both compliant with drug-likeness thresholds. Its molar refractivity (MR) (143.49) is marginally higher than the reference value of ≤120, while the topological polar surface area (TPSA) of 119.13 Å² falls just below the upper limit of 140 Å², suggesting acceptable polarity for oral absorption. Consistent with these properties, Rimegepant is predicted to exhibit high gastrointestinal (GI) absorption. The compound is identified as a P-glycoprotein (P-gp) substrate, which may influence its efflux and overall bioavailability but is not expected to

hinder absorption significantly. Importantly, Rimegepant is predicted not to penetrate the blood-brain barrier (BBB), which aligns with its peripheral mechanism of action. Regarding metabolic interactions, Rimegepant is not an inhibitor of CYP1A2, CYP2C19, CYP2C9, or CYP2D6, although it is predicted to inhibit CYP3A4, indicating a potential risk for drug–drug interactions with CYP3A4-metabolized agents. The predicted skin permeation coefficient (Log Kp = –7.93 cm/s) indicates low transdermal permeability, which is typical for orally administered small molecules. Overall, the ADME profile suggests that Rimegepant possesses favorable gastrointestinal absorption and acceptable physicochemical characteristics, though its CYP3A4 inhibitory potential and P-gp substrate status may require consideration in pharmacokinetic and clinical contexts.

Table 2. Physicochemical and pharmacokinetic properties of rimegepant using SwissADME software.

C/N	MW	HBA	HBD	MR	TPSA	GI	P-gp	BBB	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4	Log K_p
Reference Value	≤500	≤10	≤5	≤120	≤140 Å²	High	No	No	No	No	No	No	No	---
Rimegepant	534.56 g/mol	8	2	143.49	119.13 Å²	High	Yes	No	No	No	No	Yes	No	-7.93 cm/s

Rimegepant is a small-molecule antagonist of the calcitonin gene-related peptide (CGRP) receptor approved for migraine therapy, and there is currently no established pharmacophore or mechanism that links it to antidiabetic activity [50, 51]. Its off-target profile also remains insufficiently understood. For example, Rimegepant has been shown to antagonize the structurally related AMY_1 (amylin) receptor in vitro, which indicates potential risks beyond its primary therapeutic target [52]. Pharmacokinetic factors present additional concerns, as food significantly reduces its C_{max} and systemic exposure, and the compound is predominantly metabolized by CYP3A4, which raises the possibility of drug–drug interactions [53, 54].

Nevertheless, the results of this computational repurposing study have important practical implications. Rimegepant exhibited strong binding affinity for DPP4, suggesting its potential as a novel inhibitor of T2D, a completely new application compared to its established use in migraine therapy [55]. From an industrial perspective, repurposing Rimegepant may streamline drug development because the compound already has well-documented human safety data, acceptable oral bioavailability, and long-term tolerability [56, 57]. This could allow it to progress more rapidly through preclinical and clinical evaluation than newly developed molecules. In addition, this approach aligns with the broader economic value of drug repositioning, which is widely recognized as a cost-efficient and time-saving strategy in T2D drug discovery [58]. If supported by further experimental validation, the pharmaceutical industry may be able to leverage Rimegepant's existing regulatory approval and manufacturing infrastructure to facilitate its development as a therapeutic candidate for diabetes.

4. Conclusions

This study highlights Rimegepant as a promising candidate for drug repurposing as a potential DPP4 inhibitor in the treatment of type 2 diabetes. Its strong binding affinity, predicted multi-target regulatory effects, and good physicochemical and pharmacokinetics

profiles suggest that it may modulate key T2D-related pathways, offering potential therapeutic benefits beyond its current clinical indications. These findings underscore the translational potential of Rimegepant in diabetes management. However, as the results are based solely on computational predictions, further validation through MD simulations, *in vitro* enzyme assays, cell-based studies, and *in vivo* models is essential to confirm its efficacy, safety, and pharmacological relevance.

Author Contributions

Conceptualization, M.F.F.M.A.; methodology, M.R.; software, M.R.; validation, M.F.F.M.A., and M.R.; formal analysis, M.R.; investigation, M.F.F.M.A.; resources, M.F.F.M.A.; data curation, M.R.; writing—original draft preparation, M.R.; writing—review and editing, M.F.F.M.A.; visualization, M.R.; supervision, M.F.F.M.A.; project administration, M.F.F.M.A.; funding acquisition, M.F.F.M.A. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Conflicts of Interest

The authors declared that they have no conflicts of interest.

Supplementary materials

Download

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
T2D	Type 2 diabetes mellitus
DPP4	Dipeptidyl Peptidase-4
LBVS	Ligand-based virtual screening
SBVS	Structure-based virtual screening
MD	Molecular dynamics
IDF	International Diabetes Federation
C. longa	*Curcuma longa*
GLP-1	Glucagon-like peptide-1
GIP	Glucose-dependent insulinotropic polypeptide
PDB	Protein Data Bank
CB-Dock2	Cavity Detection Blind Docking 2
SMILES	Simplified Molecular Input Line Entry System
STRING	Search Tool for the Retrieval of Interacting Genes/Proteins
DAVID	Database for Annotation, Visualization, and Integrated Discovery
GO	Gene ontology
BP	Biological Process
CC	Cellular Component
MF	Molecular Function
KEGG	Kyoto Encyclopedia of Genes and Genomes
TCM	Traditional Chinese Medicine
PPI	Protein-protein interaction
IRS	Insulin receptor substrates
ADME	Absorption, distribution, metabolism, and excretion
MW	Molecular weight
HBA	Hydrogen bond acceptors
HBD	Hydrogen bond donor
TPSA	Topological polar surface area
GI	Gut intestine
BBB	Blood-brain barrier
MR	Molar refractivity
CGRP	Calcitonin gene-related peptide

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