

Structure-Based Screening and ADMET Prioritization of Bioactive Small Molecules Targeting the IGF-1 Receptor Kinase Domain: Implications for Pancreatic β -Cell Function

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ABSTRACT

The insulin-like growth factor-1 receptor (IGF1R) is involved in cell survival and metabolic signaling and has an important connection with pancreatic β -cell function. In this study, 15 bioactive compounds were screened against the human IGF1R kinase domain using molecular docking together with SwissADME and ProTox-3.0 analysis. CB-Dock2 identified five binding cavities, with P1 emerging as the preferred region for most of the compounds. The docking setup was further supported by redocking of the crystallographic BMI ligand, which reproduced a near-native pose with a minimum heavy-atom RMSD of 0.69 Å. Among the screened compounds, Puerarin showed the strongest docking score (-10.1 kcal/mol). Mangiferin and Silibinin followed with scores of -9.1 kcal/mol, while Wedelolactone, Baicalein, and Paeoniflorin also showed favorable binding scores. The ADMET results, however, showed that strong docking did not always correspond to favorable drug-like properties. Puerarin and Paeoniflorin showed no high-confidence ProTox toxicity alerts, although both had limitations related to predicted oral absorption. Several other compounds showed potential concerns involving CYP interactions or predicted respiratory, cardiac, or immunological toxicity. Mangiferin produced an unusually low predicted oral LD₅₀ of 2 mg/kg, which was treated cautiously as a model-derived result. Overall, the study identified several compounds with promising structural compatibility toward IGF1R. Puerarin was particularly notable because it combined the strongest docking result with a comparatively limited predicted toxicity profile, although its low predicted gastrointestinal absorption remains a limitation. These findings provide a useful basis for further experimental studies to confirm IGF1R binding and explore the possible effects of these compounds on pancreatic β -cell function.

Keywords: IGF1R; molecular docking; Puerarin; pancreatic β -cell; SwissADME; ProTox-3.0; ADMET; bioactive compounds.

1. Introduction

Diabetes mellitus is a major and expanding global health burden characterized by persistent disturbances in glucose homeostasis arising from impaired insulin secretion, impaired insulin action, or a combination of both. According to the 11th edition of the International Diabetes Federation Diabetes Atlas, approximately 589 million adults aged 20–79 years were living with diabetes in 2024, representing about 11.1% of the global adult population, and this number is projected to increase to approximately 853 million by 2050 [1].

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Type 2 diabetes mellitus (T2DM), which accounts for the majority of diabetes cases, develops through a progressive interaction between peripheral insulin resistance and failure of pancreatic β -cells to maintain sufficient insulin secretion. During the early stages of insulin resistance, β -cells compensate by increasing insulin production and secretion; however, persistent metabolic demand, oxidative stress, inflammatory signaling, endoplasmic-reticulum stress, and cellular aging can progressively compromise β -cell identity and secretory capacity [1,2]. Preservation of functional β -cell mass and restoration of β -cell competence therefore remain important objectives in the search for new therapeutic strategies for T2DM.

Among the signaling networks implicated in β -cell physiology, the insulin/insulin-like growth factor signaling axis is of particular interest. The insulin-like growth factor-1 receptor (IGF1R) is a transmembrane receptor tyrosine kinase closely related structurally and functionally to the insulin receptor. Ligand engagement induces receptor autophosphorylation and recruitment of intracellular signaling proteins, including insulin receptor substrate proteins, which subsequently regulate pathways such as phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and Ras/mitogen-activated protein kinase (MAPK) signaling [3]. These pathways influence cellular metabolism, survival, growth, differentiation, and adaptive responses.

The structural and functional overlap between the insulin receptor and IGF1R is particularly relevant in metabolically active tissues, including pancreatic β -cells, where coordinated insulin/IGF signaling contributes to the regulation of cellular function and glucose homeostasis [3].

Experimental genetic evidence supports an important physiological role for IGF1R in pancreatic β -cells. β -cell-specific deletion of *Igf1r* in mice produced glucose intolerance and defective glucose-stimulated insulin secretion without a corresponding reduction in β -cell mass, indicating that IGF1R signaling contributes to β -cell functional competence rather than simply controlling cell abundance [4]. In an independent conditional knockout model, loss of functional IGF1R signaling similarly impaired glucose- and arginine-stimulated insulin secretion, further demonstrating a requirement for IGF1R-mediated signaling in normal β -cell secretory responses [5]. Moreover, the IGF system has been linked to β -cell survival. Cornu and colleagues demonstrated that glucagon-like peptide-1 increased IGF1R expression and promoted an IGF-2/IGF1R autocrine signaling loop, which was required for protection of β -cells against cytokine-induced apoptosis [6]. Together, these findings establish a mechanistic relationship between IGF1R signaling, insulin secretion, and β -cell survival.

However, the role of IGF1R in β -cell biology is complex and appears to depend on cellular and physiological context. Identification of the insulin inhibitory receptor, or inceptor, demonstrated that suppression of this negative regulator increased insulin receptor-IGF1R signaling and enhanced β -cell proliferation in experimental systems [7]. In contrast, more recent work showed that reducing IGF1R signaling in adult β -cells attenuated cellular senescence, improved glucose-stimulated insulin secretion, and restored expression of genes involved in β -cell identity and function [8]. These apparently divergent findings suggest that excessive or insufficient IGF1R signaling may have different consequences depending on age, metabolic state, receptor abundance, and intracellular signaling context. Accordingly, a structure-based drug-discovery strategy should avoid assuming that ligand binding necessarily corresponds to receptor activation or a predefined biological response. It is therefore more appropriate to investigate compounds as putative IGF1R-binding modulators and subsequently determine their functional consequences experimentally.

Structural information available for IGF1R provides a strong basis for computational ligand screening. The kinase domain of human IGF1R has been structurally characterized in complex with small-molecule inhibitors, providing experimentally resolved information regarding ligand accommodation within the catalytic region [9]. Of particular relevance to the present study, Protein Data Bank entry 2OJ9 represents the human IGF1R kinase domain complexed with the benzimidazole inhibitor BMI and was determined by X-ray crystallography at a resolution of 2.00 Å [9,10]. The presence of a co-crystallized ligand provides an experimentally defined structural reference for evaluating predicted ligand-binding regions and for assessing whether a docking procedure is capable of recovering a crystallographically plausible binding orientation. Thus, the 2OJ9 structure offers a suitable platform for structure-based investigation of chemically diverse bioactive compounds targeting the IGF1R kinase domain.

Natural products and naturally derived small molecules constitute a chemically diverse source of scaffolds for early-stage drug discovery.

Numerous plant-derived compounds have been investigated for their effects on glucose metabolism, oxidative stress, inflammation, insulin secretion, and β -cell survival; however, their biological activities and pharmacological suitability vary substantially across experimental systems [2]. Molecular docking provides a comparatively rapid approach for prioritizing compounds by estimating plausible protein-ligand binding orientations and generating comparative docking scores [11]. Nevertheless, docking scores represent computational scoring estimates rather than experimentally measured binding affinities, and favorable docking alone cannot establish receptor activation, biological efficacy, or therapeutic benefit. Consequently, computational screening is strengthened when docking is combined with structural validation and assessment of pharmacokinetic and toxicological properties.

CB-Dock2 is a blind protein-ligand docking platform that integrates cavity detection, structure-based docking, and homologous-template-based information to identify potential ligand-binding regions and predict binding poses [12]. Its structure-based docking workflow incorporates the CurPocket cavity-detection algorithm and AutoDock Vina-based scoring [12,13]. CB-Dock2 has demonstrated improved binding-pose prediction performance compared with the original CB-Dock workflow and reports cavity centers, cavity volumes, docking scores, and predicted ligand poses, making it suitable for comparative evaluation of ligands across multiple potential binding regions [12]. Complementing structure-based screening with absorption, distribution, metabolism, and excretion predictions can further assist candidate prioritization. SwissADME provides computational assessment of physicochemical properties, lipophilicity, solubility, gastrointestinal absorption, blood-brain barrier permeation, P-glycoprotein behavior, cytochrome P450 inhibition, drug-likeness, and medicinal-chemistry characteristics [14]. In parallel, ProTox-3.0 enables prediction of acute oral toxicity and multiple organ- and endpoint-specific toxicity properties, allowing potential safety liabilities to be considered during computational candidate selection [15]. Accordingly, the present study employed an integrated structure-based computational strategy to evaluate 15 bioactive small molecules against the human IGF1R kinase domain. Blind molecular docking and cavity analysis were performed using CB-Dock2, followed by comparative evaluation of binding-pocket preferences and docking scores. The crystallographic BMI ligand associated with PDB 2OJ9 was additionally used for reference-ligand redocking and docking-protocol validation. Molecular docking results were subsequently integrated with SwissADME-based physicochemical, pharmacokinetic, and drug-likeness predictions and ProTox-3.0-based toxicity assessment. The overall objective was to prioritize structurally plausible IGF1R-binding bioactive compounds while simultaneously considering predicted developability and toxicity liabilities. Importantly, the computational findings were interpreted as evidence of putative molecular recognition and candidate prioritization, rather than as proof of IGF1R activation, pancreatic β -cell regeneration, antidiabetic efficacy, or *in vivo* therapeutic activity.

2. Materials and Methods

2.1. Study Design

An integrated *in silico* workflow was employed to evaluate the potential interaction of selected bioactive small molecules with the human insulin-like growth factor-1 receptor (IGF1R) kinase domain.

The study comprised receptor preparation, ligand preparation, blind molecular docking and cavity analysis using CB-Dock2, validation of the docking procedure using the crystallographic reference ligand, physicochemical and pharmacokinetic profiling using SwissADME, and toxicity prediction using ProTox-3.0. The resulting docking and ADMET parameters were subsequently evaluated comparatively for candidate prioritization.

2.2. Protein Structure Retrieval and Preparation

The X-ray crystal structure of the human IGF1R kinase domain was retrieved from the RCSB Protein Data Bank using PDB ID 2OJ9 [10]. The structure was resolved at 2.00 Å resolution and contains the IGF1R kinase domain in complex with the benzimidazole inhibitor BMI. RCSB confirms 2OJ9 as a human IGF1R structure determined by X-ray diffraction and containing BMI as the crystallographic ligand. Chain A was used for molecular docking. Prior to docking, the co-crystallized BMI ligand and 204 crystallographic water molecules were removed. The BMI ligand contained 30 crystallographic ligand-atom records. No additional heteroatoms were retained in the prepared receptor. Inspection of the PDB record identified unresolved residues at A950–A953 and A1068–A1075. The internal discontinuity at A1068–A1075 was retained without artificial reconstruction, loop modeling, or homology modeling. The same prepared receptor structure was used for all ligand docking calculations to maintain methodological consistency.

2.3. Ligand Selection and Preparation

A library of 15 bioactive compounds was selected for structure-based screening: Arctigenin, Astragaloside IV, Baicalein, Capsaicin, Cinnamaldehyde, Ginsenoside Rb1, Ginsenoside Rb2, Mangiferin, Oleanolic acid, Paeoniflorin, Puerarin, Salidroside, Silibinin, Stevioside, and Wedelolactone. The chemical identities of the compounds were verified using their corresponding PubChem Compound identifiers, and molecular structures were obtained in SDF format from the PubChem database [16]. PubChem provides standardized chemical structure records and was used to maintain consistent ligand identity throughout the study. The complete molecular structures were retained throughout the docking analysis; no ligand was truncated or chemically modified to satisfy downstream prediction-platform requirements.

2.4. Blind Molecular Docking and Binding-Cavity Analysis

Blind molecular docking was performed using CB-Dock2, which integrates protein-cavity detection with molecular docking and homologous-template information [12]. CB-Dock2 employs cavity-guided docking and incorporates AutoDock Vina-based scoring for prediction of ligand-binding poses [12,13]. Each of the 15 ligands was docked individually against the same prepared IGF1R receptor. No predefined binding site or manually assigned docking grid was imposed. Instead, CB-Dock2 automatically identified potential binding cavities.

Five CurPocket cavities were consistently detected and designated P1–P5. Their respective cavity volumes were 1995, 420, 328, 188, and 185 Å³, with center coordinates of (7.778, 1.004, 21.962), (29.499, –9.707, 14.500), (10.968, –10.274, 4.600), (–0.407, –0.983, 9.623), and (–5.996, 6.465, 12.753), respectively.

For each ligand, the Vina score obtained for all five cavities was retained.

The most negative docking score was considered the best predicted docking score for that compound, and the corresponding cavity was recorded as its preferred predicted binding pocket. Where identical minimum scores were obtained in two cavities, both pockets were retained. Docking scores were interpreted as comparative computational scoring estimates rather than experimentally measured binding free energies. Similarly, the contact residue output generated by CurPocket was treated as spatial contact information and was not interpreted as evidence of specific hydrogen bonds or other defined molecular interactions without additional structural analysis.

2.5. Reference-Ligand Redocking and Docking Validation

The co-crystallized BMI ligand from the original 2OJ9 structure was used to evaluate the ability of the docking workflow to reproduce a crystallographically observed ligand orientation. BMI was extracted from the original structure while retaining its experimental heavy-atom coordinates. Correct chemical connectivity and bond orders were assigned according to the RCSB BMI chemical definition. Ligand handling and structural comparison were performed using RDKit version 2025.09.4 [17]. This release and its software DOI are independently archived by Zenodo.

The prepared BMI ligand was redocked against the same ligand-free IGF1R receptor using CB-Dock2 under the same blind-docking strategy applied to the screening library. Five cavities were again detected, and the poses generated within the principal cavity were retained for structural comparison. Docked BMI poses were compared with the original crystallographic BMI orientation by calculating heavy-atom root-mean-square deviation (RMSD) after establishing chemically corresponding atoms between the docked and experimental structures. The minimum RMSD among the generated poses was used to assess whether the docking procedure was capable of sampling a near-native ligand orientation. The numerical validation result is reported in the Results section rather than in the methodology.

2.6. SwissADME Profiling

Physicochemical, pharmacokinetic, and drug-likeness properties were evaluated using the SwissADME web server [14]. SwissADME provides computational estimates of molecular and pharmacokinetic properties relevant to early-stage drug discovery. The recorded parameters included molecular weight, hydrogen-bond acceptors and donors, rotatable bonds, topological polar surface area, Consensus LogP, ESOL solubility, gastrointestinal absorption, blood–brain barrier permeation, P-glycoprotein substrate status, predicted CYP450 inhibition, Lipinski rule violations, bioavailability score, PAINS alerts, Brenk alerts, and synthetic accessibility. SwissADME successfully generated results for 13 of the 15 compounds. Ginsenoside Rb1 and Ginsenoside Rb2 could not be processed using their complete stereochemical representations because the input exceeded the platform's accepted input length. Their SwissADME values were therefore reported as not available (NA), and the structures were not shortened or altered.

2.7. ProTox-3.0 Toxicity Prediction

Toxicity profiling was carried out using ProTox-3.0 [15], an *in silico* toxicity-prediction platform incorporating molecular similarity and machine-learning models for acute toxicity and multiple toxicity endpoints.

For successfully processed compounds, predicted oral LD₅₀, toxicity class, average similarity, prediction accuracy, organ-toxicity endpoints, carcinogenicity, immunotoxicity, mutagenicity, cytotoxicity, clinical toxicity, and CYP-related predictions were recorded. Both the model classification and its associated prediction probability were retained. For comparative interpretation, Active predictions with probability values of ≥ 0.70 were highlighted as higher-confidence computational alerts; however, the complete Active/Inactive predictions and probability values were retained in the dataset. The ProTox documentation identifies the reported probability as the model's confidence estimate and notes that results below 0.70 are normally treated as below its display threshold. ProTox-3.0 successfully processed 13 compounds. Ginsenoside Rb1 and Ginsenoside Rb2 exceeded the platform-supported compound size and were therefore recorded as not processed (NP) rather than assigning estimated toxicity values.

2.8. Data Compilation and Comparative Analysis

Docking, SwissADME, and ProTox-3.0 outputs were compiled into a unified comparative dataset. Candidate interpretation considered the best docking score and preferred cavity together with predicted gastrointestinal absorption, drug-likeness, CYP liabilities, bioavailability, acute toxicity class, and major predicted toxicity alerts. No missing ADMET values were replaced with zero, and results from SwissADME and ProTox-3.0 were retained as outputs from independent predictive platforms. Because the study consisted of computational screening rather than replicated biological experiments, inferential statistical tests were not applied. The resulting data were interpreted descriptively for candidate prioritization only, and no docking or ADMET prediction was considered evidence of experimentally confirmed IGF1R activation, β -cell regeneration, antidiabetic activity, or clinical efficacy.

Table 2: CB-Dock2 docking scores of the screened compounds against the five IGF1R CurPockets

Compound	P1	P2	P3	P4	P5	Best score (kcal/mol)	Preferred pocket
Arctigenin	-7.3	-5.8	-6.4	-6.6	-6.7	-7.3	P1
Astragaloside IV	-6.7	-7.7	-7.7	-7.6	-7.5	-7.7	P2/P3
Baicalein	-8.4	-7.0	-7.6	-6.7	-6.4	-8.4	P1
Capsaicin	-7.6	-6.4	-6.1	-6.0	-5.1	-7.6	P1
Cinnamaldehyde	-5.9	-4.8	-5.0	-4.4	-4.4	-5.9	P1
Ginsenoside Rb1	-7.7	-6.8	-8.0	-8.1	-7.1	-8.1	P4
Ginsenoside Rb2	-8.2	-7.6	-7.6	-8.2	-7.1	-8.2	P1/P4
Mangiferin	-9.1	-7.8	-7.6	-7.4	-7.0	-9.1	P1
Oleanolic acid	-5.9	-7.6	-5.8	-7.6	-8.1	-8.1	P5
Paeoniflorin	-8.3	-7.1	-8.0	-7.0	-6.9	-8.3	P1
Puerarin	-10.1	-7.4	-8.0	-7.5	-7.4	-10.1	P1
Salidroside	-7.5	-6.6	-6.9	-6.0	-6.1	-7.5	P1
Silibinin	-9.1	-8.2	-7.8	-7.6	-7.1	-9.1	P1
Stevioside	-6.8	-7.6	-7.5	-7.7	-8.0	-8.0	P5
Wedelolactone	-8.7	-7.1	-7.8	-6.6	-6.4	-8.7	P1

Among all compounds, Puerarin produced the most negative docking score (-10.1 kcal/mol) and favored P1. Mangiferin and Silibinin each showed a best docking score of -9.1 kcal/mol in P1, followed by Wedelolactone at -8.7 kcal/mol, Baicalein at -8.4 kcal/mol, and Paeoniflorin at -8.3 kcal/mol.

P1 was the sole preferred cavity for 10 compounds: Arctigenin, Baicalein, Capsaicin, Cinnamaldehyde, Mangiferin, Paeoniflorin, Puerarin, Salidroside, Silibinin, and Wedelolactone. Ginsenoside Rb2 exhibited an equal best score in P1 and P4. In contrast, Ginsenoside Rb1 preferentially occupied P4, Oleanolic acid and Stevioside favored P5, whereas Astragaloside IV produced identical best scores in P2 and P3.

3. Results

3.1. IGF1R Structure Preparation and Binding-Cavity Detection

The human IGF1R kinase-domain structure 2OJ9, resolved by X-ray diffraction at $2.00 \text{ \AA}$, was used for molecular docking. Chain A was retained, whereas the co-crystallized BMI ligand and 204 crystallographic water molecules were removed before ligand screening. The BMI ligand contained 30 crystallographic ligand atom records. Inspection of the deposited structure identified unresolved residues at A950–A953 and A1068–A1075. These regions were retained without computational reconstruction. CB-Dock2 consistently identified five CurPocket cavities across all 15 ligand-docking runs. P1 was the largest cavity, with a volume of $1995 \text{ \AA}^3$, followed by P2, P3, P4, and P5 with respective volumes of 420, 328, 188, and $185 \text{ \AA}^3$. The pocket-center coordinates remained unchanged across individual docking runs.

Table 1: Structural characteristics of the IGF1R CurPocket cavities

Pocket	Volume ($\text{\AA}^3$)	Center X	Center Y	Center Z
P1	1995	7.778	1.004	21.962
P2	420	29.499	-9.707	14.500
P3	328	10.968	-10.274	4.600
P4	188	-0.407	-0.983	9.623
P5	185	-5.996	6.465	12.753

Because several P2 and P3 cavity-associated residue lists were located close to the unresolved A1068–A1075 region, docking results involving these cavities were interpreted cautiously.

3.2. Comparative Molecular Docking of Bioactive Compounds against IGF1R

All 15 compounds generated docked poses within the five detected CurPocket cavities. The best docking scores ranged from -5.9 to -10.1 kcal/mol, demonstrating considerable variation in predicted ligand–receptor complementarity.

3.3. Validation of the Docking Procedure Using the Crystallographic BMI Ligand

The crystallographic BMI ligand was blind-redocked against the prepared IGF1R receptor using the same CB-Dock2 workflow. BMI produced a docking score of -8.5 kcal/mol in C1, the $1995 \text{ \AA}^3$ cavity corresponding geometrically to P1. An equivalent score of -8.5 kcal/mol was also observed in C2, indicating that docking score alone was insufficient to identify the crystallographically relevant pose.

Nine BMI poses generated within C1 were compared with the original crystallographic ligand coordinates. Heavy-atom RMSD values of 7.88, 4.48, 0.69, 2.48, 6.84, 6.94, 8.46, 4.41, and 5.15 Å were obtained for Models 1–9, respectively. Model 3 showed the minimum RMSD of 0.69 Å, indicating successful recovery of a near-native crystallographic orientation.

Table 3: BMI reference-ligand redocking validation

Parameter	Result
Reference ligand	BMI (A301)
Reference structure	PDB 2OJ9
Relevant cavity	C1
Cavity volume	1995 Å ³
C1 docking score	−8.5 kcal/mol
Number of C1 poses evaluated	9
Near-native pose	Model 3
Minimum heavy-atom RMSD	0.69 Å
RMSD of first-listed pose	7.88 Å

These findings demonstrate that the blind-docking procedure was capable of sampling a near-native BMI binding orientation, although the near-native conformation was not the first-listed pose.

Numerically, Puerarin (−10.1 kcal/mol), Mangiferin (−9.1 kcal/mol), Silibinin (−9.1 kcal/mol), and Wedelolactone (−8.7 kcal/mol) produced more negative docking scores than the BMI C1 score of −8.5 kcal/mol. These values were interpreted as comparative docking scores rather than experimental binding-affinity measurements.

3.4. SwissADME Physicochemical and Pharmacokinetic Profiling

SwissADME successfully generated predictions for 13 of the 15 compounds. Ginsenoside Rb1 and Ginsenoside Rb2 were not processed because their complete stereochemical input representations exceeded the accepted platform input limit; therefore, their corresponding values were recorded as not available.

Table 4: Selected SwissADME physicochemical and pharmacokinetic parameters

Compound	MW	TPSA (Å ²)	Consensus LogP	GI absorption	BBB permeant	P-gp substrate	Lipinski violations	Bioavailability score
Arctigenin	372.41	74.22	3.13	High	Yes	No	0	0.55
Astragaloside IV	784.97	228.22	1.35	Low	No	Yes	3	0.17
Baicalein	270.24	90.90	1.73	High	No	No	0	0.55
Capsaicin	305.41	58.56	3.53	High	Yes	No	0	0.55
Cinnamaldehyde	132.16	17.07	1.98	High	Yes	No	0	0.55
Ginsenoside Rb1	NA	NA	NA	NA	NA	NA	NA	NA
Ginsenoside Rb2	NA	NA	NA	NA	NA	NA	NA	NA
Mangiferin	422.34	201.28	−0.65	Low	No	No	2	0.17
Oleanolic acid	456.70	57.53	6.16	Low	No	No	1	0.85
Paeoniflorin	480.46	164.37	−0.12	Low	No	Yes	1	0.55
Puerarin	416.38	160.82	−0.30	Low	No	No	1	0.55
Salidroside	300.30	119.61	−0.39	High	No	No	0	0.55
Silibinin	482.44	155.14	1.60	Low	No	No	0	0.55
Stevioside	804.87	294.98	−1.20	Low	No	Yes	3	0.17
Wedelolactone	314.25	113.27	2.01	High	No	No	0	0.55

High gastrointestinal absorption was predicted for Arctigenin, Baicalein, Capsaicin, Cinnamaldehyde, Salidroside, and Wedelolactone, whereas the remaining successfully processed compounds showed low predicted gastrointestinal absorption. Only Arctigenin, Capsaicin, and Cinnamaldehyde were predicted to be BBB permeant. Astragaloside IV, Paeoniflorin, and Stevioside were predicted to be P-glycoprotein substrates. Seven compounds, such as Arctigenin, Baicalein, Capsaicin, Cinnamaldehyde, Salidroside, Silibinin, and Wedelolactone, showed no Lipinski rule violations. Oleanolic acid, Paeoniflorin, and Puerarin showed one violation each; Mangiferin showed two violations, whereas Astragaloside IV and Stevioside showed three violations each.

Table 5: ProTox-3.0 predicted acute oral toxicity

Compound	Predicted LD ₅₀ (mg/kg)	Toxicity class	Similarity (%)	Prediction accuracy (%)
Arctigenin	1500	4	76.64	69.26
Astragaloside IV	23,000	6	58.96	67.38
Baicalein	3919	5	81.74	70.97
Capsaicin	47	2	100	100
Cinnamaldehyde	1850	4	100	100
Ginsenoside Rb1	NP	NP	NP	NP
Ginsenoside Rb2	NP	NP	NP	NP
Mangiferin	2	1	100	100
Oleanolic acid	2000	4	100	100
Paeoniflorin	4000	5	74.50	69.26
Puerarin	832	4	62.03	68.07
Salidroside	5000	5	69.01	68.07
Silibinin	2000	4	76.44	69.26
Stevioside	4000	5	75.61	69.26
Wedelolactone	3800	5	77.66	69.26

NP: not processed because of the platform molecular-size limitation.

SwissADME predicted Arctigenin to inhibit CYP2C9, CYP2D6, and CYP3A4; Baicalein and Capsaicin to inhibit CYP1A2, CYP2D6, and CYP3A4; Salidroside to inhibit CYP1A2; Silibinin to inhibit CYP3A4; and Wedelolactone to inhibit CYP1A2, CYP2D6, and CYP3A4. These predictions were retained independently from ProTox-derived CYP outputs.

3.5. ProTox-3.0 Acute Oral Toxicity Predictions

ProTox-3.0 successfully generated toxicity predictions for 13 compounds. Ginsenoside Rb1 and Ginsenoside Rb2 were not processed because they exceeded the platform-supported molecular-size limit.

Astragaloside IV showed the highest predicted LD₅₀ at 23,000 mg/kg and was assigned toxicity class 6. Baicalein, Paeoniflorin, Salidroside, Stevioside, and Wedelolactone were assigned toxicity class 5. Arctigenin, Cinnamaldehyde, Oleanolic acid, Puerarin, and Silibinin were assigned class 4, whereas Capsaicin was assigned class 2 with a predicted LD₅₀ of 47 mg/kg. The corrected Arctigenin result showed a predicted LD₅₀ of 1500 mg/kg, class 4, average similarity of 76.64%, and prediction accuracy of 69.26%.

Mangiferin produced an unusual ProTox-3.0 model output of 2 mg/kg, corresponding to toxicity class 1, with reported similarity and prediction accuracy of 100%. This value was retained exactly as generated by the prediction platform.

3.6. Predicted Toxicity and CYP-Related Alerts

For comparative interpretation, ProTox Active predictions with model probabilities of ≥ 0.70 were highlighted as higher-confidence computational alerts.

Table 6: Higher-confidence ProTox-3.0 Active predictions

Compound	Toxicity alerts (P ≥ 0.70)	CYP alerts (P ≥ 0.70)
Arctigenin	Immunotoxicity 0.98	CYP2C9 0.78
Astragaloside IV	Immunotoxicity 0.99	None
Baicalein	Respiratory toxicity 0.83	CYP1A2 1.00; CYP2C19 0.77; CYP2C9 0.99
Capsaicin	Respiratory toxicity 0.79; Carcinogenicity 0.71; Immunotoxicity 0.86	CYP1A2 0.93; CYP2C19 0.94; CYP2C9 0.76; CYP2D6 0.70; CYP3A4 0.99
Cinnamaldehyde	Neurotoxicity 0.73; Cardiotoxicity 0.91; Mutagenicity 0.72	None
Ginsenoside Rb1	NP	NP
Ginsenoside Rb2	NP	NP
Mangiferin	None	None
Oleanolic acid	Respiratory toxicity 0.89; Cardiotoxicity 0.71; Immunotoxicity 0.79	None
Paeoniflorin	None	None
Puerarin	None	None
Salidroside	Nephrotoxicity 0.77	None
Silibinin	Cardiotoxicity 0.72; Immunotoxicity 0.97	CYP2C9 0.81
Stevioside	Cardiotoxicity 1.00; Immunotoxicity 0.97	None
Wedelolactone	Respiratory toxicity 0.78	CYP2C9 0.71

Arctigenin showed high-confidence immunotoxicity and CYP2C9 predictions with probabilities of 0.98 and 0.78, respectively. Its nephrotoxicity prediction was Active at 0.62 but remained below the predefined ≥ 0.70 reporting threshold.

Baicalein and Capsaicin exhibited multiple CYP-related predictions, while Oleanolic acid, Silibinin, and Stevioside showed several higher-confidence toxicity alerts. In contrast, Puerarin and Paeoniflorin showed no Active prediction with a probability ≥ 0.70 . Mangiferin also showed no individual endpoint prediction reaching this threshold despite its unusually low predicted acute oral LD₅₀.

3.7. Integrated Docking–ADMET Assessment

Integration of the docking, SwissADME, and ProTox-3.0 results demonstrated substantial differences among the screened compounds and showed that no molecule was uniformly favorable across all computational parameters.

Table 7: Integrated docking–ADMET profile of the screened compounds

Compound	Best docking score	Pocket	GI absorption	Lipinski violations	Bioavailability score	LD ₅₀ (mg/kg)	Class	Major higher-confidence alerts
Arctigenin	-7.3	P1	High	0	0.55	1500	4	Immunotoxicity; CYP2C9
Astragaloside IV	-7.7	P2/P3	Low	3	0.17	23,000	6	Immunotoxicity
Baicalein	-8.4	P1	High	0	0.55	3919	5	Respiratory toxicity; CYP alerts
Capsaicin	-7.6	P1	High	0	0.55	47	2	Multiple toxicity/CYP alerts
Cinnamaldehyde	-5.9	P1	High	0	0.55	1850	4	Neurotoxicity; cardiotoxicity; mutagenicity
Ginsenoside Rb1	-8.1	P4	NA	NA	NA	NP	NP	Not processed
Ginsenoside Rb2	-8.2	P1/P4	NA	NA	NA	NP	NP	Not processed
Mangiferin	-9.1	P1	Low	2	0.17	2	1	None ≥ 0.70
Oleanolic acid	-8.1	P5	Low	1	0.85	2000	4	Respiratory toxicity; cardiotoxicity; immunotoxicity
Paeoniflorin	-8.3	P1	Low	1	0.55	4000	5	None ≥ 0.70
Puerarin	-10.1	P1	Low	1	0.55	832	4	None ≥ 0.70
Salidroside	-7.5	P1	High	0	0.55	5000	5	Nephrotoxicity
Silibinin	-9.1	P1	Low	0	0.55	2000	4	Cardiotoxicity; immunotoxicity; CYP2C9
Stevioside	-8.0	P5	Low	3	0.17	4000	5	Cardiotoxicity; immunotoxicity
Wedelolactone	-8.7	P1	High	0	0.55	3800	5	Respiratory toxicity; CYP2C9

Puerarin combined the most negative docking score (-10.1 kcal/mol) with no ProTox Active prediction reaching the ≥ 0.70 threshold; however, SwissADME predicted low gastrointestinal absorption, a TPSA of 160.82 Å², and one Lipinski-rule violation. Paeoniflorin also showed no higher-confidence ProTox alert and produced a docking score of -8.3 kcal/mol in P1, although low gastrointestinal absorption and P-glycoprotein substrate behavior were predicted.

Wedelolactone combined a relatively strong docking score of -8.7 kcal/mol with high predicted gastrointestinal absorption and no Lipinski violations, but respiratory toxicity and CYP2C9 activity were predicted at 0.78 and 0.71, respectively.

Silibinin and Mangiferin both produced docking scores of -9.1 kcal/mol but differed substantially in predicted developability. Silibinin showed low gastrointestinal absorption together with cardiotoxicity, immunotoxicity, and CYP2C9 alerts, whereas Mangiferin showed low gastrointestinal absorption,

two Lipinski violations, a bioavailability score of 0.17, and the unusually low ProTox-predicted LD₅₀ of 2 mg/kg.

Overall, the combined computational analysis identified several structurally plausible IGF1R-binding candidates with distinct pharmacokinetic and toxicity trade-offs. The results therefore support comparative candidate prioritization for subsequent experimental investigation rather than confirmation of IGF1R activation, pancreatic β -cell regeneration, antidiabetic efficacy, or in vivo safety.

4. Discussion

The present study integrated blind molecular docking, crystallographic reference-ligand redocking, and predictive ADMET profiling to evaluate 15 bioactive compounds against the human IGF1R kinase domain. The major structural finding was the preferential localization of most screened compounds within P1, the largest detected cavity. Ten compounds showed P1 as their sole best-scoring pocket, while Ginsenoside Rb2 showed an equal preference for P1 and P4. Importantly, blind redocking of the crystallographic BMI ligand recovered a near-native pose within the corresponding C1/P1 region with a minimum heavy-atom RMSD of 0.69 Å, supporting the ability of the docking workflow to sample the experimentally observed ligand-binding region.

4.1. Structural Significance of the Predominant P1 Binding Cavity

The predominance of P1 among the screened ligands is particularly relevant because the crystallographic BMI ligand was successfully reproduced within the same cavity. BMI is a benzimidazole-class IGF1R kinase inhibitor, and the original structural and structure–activity studies demonstrated that this chemical series can occupy the IGF1R kinase region and inhibit receptor kinase activity [9]. Therefore, recovery of a near-native BMI conformation within C1 provides an experimentally anchored structural reference for interpreting the P1 docking results.

Nevertheless, occupation of the same cavity should not be interpreted as evidence that the screened molecules reproduce the pharmacological action of BMI. Molecular docking evaluates geometric and energetic compatibility within a protein cavity but does not determine whether a bound molecule functions as an agonist, antagonist, inhibitor, partial modulator, or pharmacologically neutral binder. This distinction is particularly important for IGF1R because β -cell studies indicate that the biological consequences of altering insulin/IGF signaling can vary with receptor abundance, metabolic state, cellular age, and signaling context [4–8]. Accordingly, the present findings support the identification of putative IGF1R-binding molecules, rather than assignment of a specific functional mode of receptor regulation.

The alternative cavity preference observed for several structurally larger compounds also deserves consideration. Astragaloside IV favored P2/P3, Ginsenoside Rb1 favored P4, whereas Oleanolic acid and Stevioside favored P5. Ginsenoside Rb2 exhibited equal best scores in P1 and P4. These differences indicate that blind docking captured ligand-dependent spatial preferences rather than forcing all molecules into a single predefined site. However, P2 and P3 predictions require particular caution because their cavity-associated residue lists extend close to the unresolved A1068–A1075 segment of the experimental structure.

4.2. Puerarin as a Structurally Prominent Candidate

Among the 15 compounds, Puerarin produced the most negative docking score (–10.1 kcal/mol) and localized to P1. It also showed no ProTox Active prediction reaching the predefined probability threshold of 0.70. However, its SwissADME profile revealed low predicted gastrointestinal absorption, a TPSA of 160.82 Å², and one Lipinski rule violation, demonstrating that favorable docking does not necessarily correspond to favorable oral developability.

The biological relevance of Puerarin is strengthened by independent experimental evidence demonstrating protective effects on pancreatic β -cells. Li et al. reported that Puerarin reduced β -cell apoptosis, increased β -cell mass, improved glucose-stimulated insulin secretion, and promoted β -cell survival through the PI3K/Akt pathway in experimental models [18]. A subsequent study demonstrated that Puerarin improved β -cell survival in obese diabetic mice through enhancement of GLP-1R signaling and downstream Akt activation [19].

These findings are mechanistically interesting because PI3K/Akt signaling is also an important downstream component of the insulin/IGF signaling network discussed in relation to IGF1R [3]. However, convergence on Akt signaling does not demonstrate that the reported β -cell effects of Puerarin are mediated through direct IGF1R binding. The present docking result therefore introduces a testable structural hypothesis that would require receptor-specific biochemical or cellular validation.

The predicted low gastrointestinal absorption of Puerarin is also consistent with published pharmacokinetic evidence. Oral Puerarin has been reported to exhibit poor oral bioavailability, and formulation or matrix effects can substantially alter its systemic exposure [23]. Thus, even if future studies confirm IGF1R-associated activity, optimization of delivery or formulation may be necessary to translate molecular activity into useful systemic exposure.

4.3. Interpretation of Other Strongly Docked Bioactive Compounds

Mangiferin and Silibinin produced the second-most-negative docking scores in the present dataset, each reaching –9.1 kcal/mol in P1, while Wedelolactone showed –8.7 kcal/mol, Baicalein –8.4 kcal/mol, and Paeoniflorin –8.3 kcal/mol. Despite their relatively favorable docking scores, their predicted ADMET characteristics differed markedly, emphasizing the importance of avoiding docking-score-only candidate selection. Silibinin is notable because experimental studies independently support β -cell-protective activity. Silibinin has been shown to protect INS-1 pancreatic β -cells against cytokine-induced damage, with estrogen-receptor-associated effects on insulin synthesis, secretion, autophagy, and apoptosis [21]. Further work demonstrated that Silibinin enhanced β -cell viability, insulin biosynthesis, and insulin secretion under glucolipotoxic conditions through an ER α /Nrf2-associated antioxidative mechanism [22]. These observations provide biological support for considering Silibinin relevant to β -cell physiology, although they do not establish IGF1R as its molecular target. In the present analysis, its potential was tempered by predicted low GI absorption and higher-confidence ProTox alerts for cardiotoxicity, immunotoxicity, and CYP2C9 activity.

Baicalein combined a docking score of –8.4 kcal/mol with high predicted GI absorption, no Lipinski violations, and a bioavailability score of 0.55.

Experimental work has previously shown that Baicalein improved glucose tolerance, glucose-stimulated insulin secretion, β -cell survival, and islet mass in obese diabetic mouse models and enhanced viability and insulin secretion in insulin-secreting cells and human islets [20]. Nevertheless, the current ProTox analysis identified respiratory toxicity and CYP-related predictions, illustrating the need to evaluate potential metabolic or toxicity liabilities alongside biological plausibility.

Wedelolactone showed a comparatively favorable balance between docking and selected SwissADME characteristics, including a docking score of -8.7 kcal/mol, high predicted GI absorption, and no Lipinski violations. However, respiratory toxicity and CYP2C9 activity were predicted with probabilities of 0.78 and 0.71, respectively. Thus, the compound remains structurally interesting but cannot be prioritized from docking alone.

Paeoniflorin presented a different profile: its docking score of -8.3 kcal/mol was accompanied by no ProTox Active prediction ≥ 0.70 , but predicted GI absorption was low and P-glycoprotein substrate behavior was observed. These examples collectively demonstrate that structurally favorable ligand-IGF1R docking can coexist with substantial pharmacokinetic limitations.

4.4. Discordance between the Mangiferin Toxicity Prediction and Published Evidence

Mangiferin represents the most important discordant result in the current ADMET dataset. It showed a relatively strong docking score of -9.1 kcal/mol in P1, but ProTox-3.0 predicted an oral LD₅₀ of only 2 mg/kg, corresponding to toxicity class 1 with reported similarity and prediction accuracy of 100%.

This value should be interpreted cautiously because it differs substantially from the broader published safety literature. A review addressing Mangiferin absorption, bioavailability, and safety reported that preclinical doses below approximately 2000 mg/kg were generally considered non-toxic across available studies [24]. Furthermore, a GLP/OECD-compliant toxicological evaluation of a mango-leaf extract containing 60% Mangiferin reported no treatment-related toxicity in a 90-day rat study at doses up to 2000 mg/kg body weight/day, establishing that dose as the NOAEL for the tested extract [25]. The latter study evaluated a Mangiferin-rich extract rather than purified Mangiferin and therefore cannot be used to assign an experimental LD₅₀ to the isolated compound. Nevertheless, the large discrepancy between the computational estimate and published experimental safety observations demonstrates an important limitation of relying on a single toxicity-prediction model. The 2 mg/kg value was therefore retained exactly as generated by ProTox-3.0 but should be considered a model-derived outlier requiring experimental verification, rather than an experimentally established acute toxicity value.

4.5. Importance of Integrating Docking with Predicted Developability

The present findings demonstrate why structure-based screening should not be interpreted through docking scores in isolation. For example, Puerarin exhibited the strongest docking score but low predicted GI absorption; Silibinin combined strong docking with several toxicity alerts; Baicalein showed a favorable oral-property profile but multiple CYP-related predictions; and Wedelolactone combined high predicted GI absorption with selected toxicity liabilities.

Conversely, Astragaloside IV exhibited a relatively high predicted acute LD₅₀ but showed three Lipinski violations, low GI absorption, P-glycoprotein substrate behavior, and a bioavailability score of 0.17.

The large glycosides also illustrate limitations imposed by chemical size and complexity. Complete SwissADME and ProTox-3.0 outputs could not be obtained for Ginsenosides Rb1 and Rb2, and their absence from the integrated ADMET comparison reflects platform restrictions rather than favorable or unfavorable biological properties. Missing computational data should therefore not be interpreted as evidence of safety.

Differences were also observed between SwissADME and ProTox CYP predictions. Such discrepancies are expected because the two platforms use distinct predictive frameworks and endpoints [14,15]. For this reason, CYP outputs from the two systems were retained independently rather than merged into an artificial consensus classification.

4.6. Biological Interpretation in the Context of Pancreatic β -Cell Function

A central consideration in interpreting these results is the relationship between IGF1R and β -cell physiology. Genetic and experimental studies have demonstrated that IGF1R participates in β -cell secretory function and survival [4–6]. At the same time, more recent work indicates that the biological response to modulation of the insulin/IGF signaling axis is context-dependent [7,8]. Consequently, identification of a molecule capable of occupying an IGF1R kinase-domain cavity does not establish whether it would enhance or suppress receptor signaling in β -cells.

The current computational results should therefore be viewed as a structure-based prioritization framework. Puerarin is particularly notable because it combined the strongest docking result with existing experimental evidence of β -cell protection through PI3K/Akt and GLP-1R/Akt signaling [18,19]. Baicalein and Silibinin also possess independent experimental evidence of β -cell-protective effects [20–22]. However, none of these previous studies demonstrates that their β -cell actions occur through direct IGF1R binding.

Accordingly, the present work does not establish that Puerarin or any other screened molecule activates IGF1R, stimulates β -cell regeneration, or exerts antidiabetic activity through IGF1R. Instead, it identifies a subset of bioactive molecules with structurally plausible IGF1R binding and defines their predicted pharmacokinetic and toxicity trade-offs. These observations provide a rational basis for subsequent receptor-specific biochemical and β -cell-based experimental evaluation.

Overall, the combined results suggest that Puerarin, Mangiferin, Silibinin, Wedelolactone, Baicalein, and Paeoniflorin warrant particular structural consideration based on their docking behavior, although their relative experimental value cannot be determined from docking alone. Among these compounds, differences in predicted absorption, drug-likeness, and toxicity substantially modify the interpretation of docking strength. The study therefore supports an integrated rather than score-driven strategy for prioritizing bioactive molecules targeting the IGF1R kinase domain.

5. Study Limitations

The present study was entirely computational, and the findings should therefore be interpreted as predictive rather than experimentally confirmed.

The CB-Dock2/Vina scores provide comparative estimates of ligand–receptor compatibility but do not represent experimentally measured binding affinities and cannot establish whether a compound activates, inhibits, or otherwise functionally modulates IGF1R. The IGF1R structure used for docking, PDB 2OJ9, contains unresolved residues at A950–A953 and A1068–A1075. Because some P2 and P3 cavity-associated residues are located near the internal A1068–A1075 gap, results involving these pockets should be interpreted cautiously. No artificial reconstruction of the missing residues was performed.

Reference-ligand redocking recovered a near-native BMI orientation with a minimum heavy-atom RMSD of 0.69 Å, supporting the ability of the docking workflow to sample the experimentally observed binding mode. However, this near-native conformation was not the first-listed pose, so the validation supports pose recovery rather than perfect pose ranking. SwissADME and ProTox-3.0 outputs are also model-derived predictions and should not be considered equivalent to experimental pharmacokinetic or toxicological data. Ginsenoside Rb1 and Ginsenoside Rb2 could not be fully evaluated because of platform-specific size/input limitations. In addition, the ProTox-3.0 prediction for Mangiferin ($LD_{50} = 2$ mg/kg; toxicity class 1) was markedly different from published safety observations and was therefore treated as a model-derived outlier requiring experimental confirmation. Overall, the present findings are best interpreted as a candidate-prioritization framework. Experimental studies are required to confirm IGF1R binding, receptor-specific functional effects, β -cell responses, and the pharmacological relevance of the prioritized compounds.

6. Conclusion

This study screened 15 bioactive compounds against the human IGF1R kinase domain using molecular docking, SwissADME, and ProTox-3.0. Most compounds preferred the P1 cavity, and redocking of the crystallographic BMI ligand reproduced a near-native pose with a minimum RMSD of 0.69 Å, supporting the reliability of the docking setup.

Among the tested compounds, Puerarin showed the strongest docking score (−10.1 kcal/mol), followed by Mangiferin and Silibinin (−9.1 kcal/mol), Wedelolactone (−8.7 kcal/mol), Baicalein (−8.4 kcal/mol), and Paeoniflorin (−8.3 kcal/mol). The ADMET results, however, showed that strong docking did not always go together with favorable drug-like properties. Puerarin, Paeoniflorin, Mangiferin, and Silibinin were predicted to have low gastrointestinal absorption, while Wedelolactone and Baicalein showed high predicted absorption and no Lipinski violations.

The toxicity analysis further helped distinguish the compounds. Puerarin and Paeoniflorin showed no high-confidence ProTox toxicity alerts, whereas several other compounds showed predicted liabilities related to respiratory toxicity, cardiotoxicity, immunotoxicity, or CYP interactions. Importantly, none of the successfully analyzed compounds showed a high-confidence cytotoxicity prediction; Stevioside showed cytotoxicity only at a lower probability. Mangiferin produced an unusually low predicted LD_{50} of 2 mg/kg, and this result should therefore be interpreted cautiously as a model-derived prediction rather than confirmed toxicity.

Overall, Puerarin appeared to be the most interesting compound from the combined docking and toxicity perspective, although its predicted low oral absorption remains an important limitation.

Other compounds, particularly Wedelolactone, Baicalein, Silibinin, Mangiferin, and Paeoniflorin, also showed promising structural compatibility with IGF1R but presented different pharmacokinetic or toxicity concerns. These findings provide a useful basis for selecting compounds for further study. Experimental work will now be required to confirm actual IGF1R binding, determine whether these molecules activate or inhibit the receptor, and evaluate their effects on pancreatic β -cell function.

Declaration of Generative AI Use

Generative AI tools were used solely for language editing, grammar correction, and improvement of the clarity and readability of the manuscript. The authors take full responsibility for the originality, accuracy, interpretation, and final content of the article.

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