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Article

In Silico Evaluation of Gynura divaricata Phytochemicals as PTP1B (1T49) Inhibitors for Antidiabetic Therapy

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Abstract. Effective management of type 2 diabetes mellitus (T2DM) requires therapeutic agents that can improve insulin sensitivity by modulating key molecular targets such as Protein Tyrosine Phosphatase 1B (PTP1B). However, the potential of *Gynura divaricata* phytochemicals as natural PTP1B inhibitors remains insufficiently characterized, despite the plant's reported antidiabetic activity. Therefore, systematic computational screening is needed to identify promising compounds and prioritize candidates for further experimental evaluation. Such prioritization is important to reduce experimental burden and accelerate discovery of plant-derived antidiabetic leads. This study aimed to evaluate selected phytochemicals from *G. divaricata* as potential PTP1B inhibitors using molecular docking, drug-likeness assessment, and ADMET prediction. Docking was performed against PTP1B (PDB ID: 1T49), followed by redocking validation and pharmacokinetic analysis. Among the tested compounds, 3,5-dicaffeoylquinic acid showed the strongest binding affinity, with a docking score of −6.806 kcal/mol and an RMSD of 1.614 Å, followed by 3,4-dicaffeoylquinic acid (−6.383 kcal/mol). Redocking produced an RMSD of 1.388 Å, confirming protocol reliability. ADMET prediction showed intestinal absorption ranging from 17.004% to 77.207%, while 3,5-dicaffeoylquinic acid was predicted to be non-hepatotoxic, AMES-negative, and non-inhibitory toward major CYP enzymes. These findings support caffeoylquinic acid derivatives as promising candidates for further in vitro and in vivo antidiabetic studies.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting primarily from insulin resistance and progressive pancreatic β-cell dysfunction [1-2]. Insulin resistance disrupts glucose utilization and metabolic homeostasis and is closely associated with impaired insulin receptor signaling [2-4]. Protein tyrosine phosphatase 1B (PTP1B), encoded by the *PTPN1* gene, is a major negative regulator of insulin signaling because it dephosphorylates the activated insulin receptor and downstream signaling substrates [5-6]. Consequently, PTP1B inhibition has emerged as a promising strategy for improving insulin sensitivity and glucose homeostasis. However, the development of effective PTP1B inhibitors remains challenging because of difficulties related to target selectivity, cellular permeability, and oral bioavailability [6-7].

Natural products provide structurally diverse molecules that may serve as alternative sources of antidiabetic agents [6],[8]. *Gynura divaricata* (L.) DC. is a medicinal plant with experimentally reported hypoglycemic activity, and recent bioactivity-guided studies have further supported its potential as a source of antidiabetic compounds [9]. Phytochemical investigations have identified several phenolic constituents, including caffeoylquinic acid derivatives, kaempferol, quercetin, and related flavonoids [10]. Importantly, previous experimental studies demonstrated that several caffeoylquinic acid derivatives isolated from *G. divaricata*, including 3,5-dicaffeoylquinic acid and 4,5-dicaffeoylquinic acid, inhibited PTP1B *in vitro*, with the number and position of caffeoyl groups influencing inhibitory activity [11].

The compounds included in the screening were selected because they represent major phenolic constituents and structurally related derivatives reported in *G. divaricata*, particularly caffeoylquinic acid derivatives together with representative flavonoids such as kaempferol and quercetin. They were prioritized based on their occurrence in the plant, reported antidiabetic or enzyme-inhibitory activities, structural diversity, and previous evidence of PTP1B inhibition for several caffeoylquinic acid derivatives [10-11].

Recent research has increasingly combined molecular docking, drug-likeness evaluation, and ADMET prediction to prioritize potential PTP1B inhibitors before experimental validation [6-7]. At the same time, recent investigations of *G. divaricata* have primarily focused on hypoglycemic activity, bioactive compound isolation, α-glucosidase inhibition, and glucose metabolism [9]. Despite these advances, comparative information on the molecular interactions of major *G. divaricata* phytochemicals with PTP1B and their predicted pharmacokinetic characteristics remains limited. Therefore, the unresolved issue is not whether *G. divaricata* possesses antidiabetic activity, but which of its representative phytochemicals exhibit the most favorable combination of PTP1B binding and drug-like properties.

The crystal structure of human PTP1B with PDB ID 1T49 provides an experimentally characterized model for structure-based analysis of allosteric inhibition. The structure was determined at 1.90 Å resolution and contains a co-crystallized allosteric inhibitor, providing a suitable framework

for evaluating ligand interactions with the PTP1B allosteric region [12]. Accordingly, this study aimed to evaluate selected *G. divaricata* phytochemicals as potential PTP1B inhibitors using molecular docking, complemented by drug-likeness and ADMET analyses. The novelty of this study lies in the integrated comparative evaluation of caffeoylquinic acid derivatives and representative flavonoids against PTP1B (PDB ID: 1T49), combining molecular binding analysis with pharmacokinetic profiling to prioritize candidates for subsequent experimental validation.

2. Method

2.1. Protein Preparation

The three-dimensional structure of human Protein Tyrosine Phosphatase 1B (PTP1B; PDB ID: 1T49) was retrieved from the RCSB Protein Data Bank. This X-ray structure contains an allosteric inhibitor and has been widely used in recent PTP1B docking studies [13-14]. The structure was resolved at 1.90 Å, with the co-crystallized inhibitor identified as ligand 892 [12],[15]. The native ligand was used to define the experimentally characterized allosteric site and to support docking validation [13-14].

Protein preparation was performed using Molecular Operating Environment (MOE). Crystallographic water molecules and non-essential heteroatoms or ions were removed, while ligand 892 was initially retained to identify the binding pocket and subsequently removed before docking. Similar MOE-based workflows apply solvent removal, hydrogen addition, protonation adjustment, and structural optimization prior to docking [16-17]. Hydrogen atoms were added, ionizable residues were protonated at pH 7.4 using Protonate 3D, and the structure was minimized using the Amber10 force field to reduce unfavorable contacts and optimize receptor geometry [16-17].

2.2. Ligand Preparation

Ten phytochemicals were evaluated: 5-O-caffeoylquinic acid, 5-O-feruloylquinic acid, methyl 5-O-caffeoylquinate, methyl 3,4-dicaffeoylquinate, methyl 4,5-dicaffeoylquinate, kaempferol, quercetin, 3,4-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid, and 4,5-dicaffeoylquinic acid. These compounds represent caffeoylquinic-acid derivatives and flavonoids associated with *Gynura divaricata*. Recent studies confirmed major caffeoylquinic-acid derivatives in this species [9], while earlier phytochemical investigations identified quercetin, kaempferol, and related phenolics [10]. Several caffeoylquinic-acid derivatives isolated from *G. divaricata* have also demonstrated PTP1B inhibitory activity [11], and recent reviews further support these compound classes as major bioactive constituents [20].

PTP1B was treated as the receptor, whereas the native ligand 892 from PDB 1T49 was used as the reference ligand for validation [13-14]. Test-ligand structures were obtained in SDF or SMILES format, converted to three-dimensional structures in MOE, protonated at pH 7.4, and minimized using Amber10 [16-17]. Ligand flexibility was addressed through LowModeMD conformational sampling, and low-energy conformers were retained for docking [18]. The native ligand was prepared using the same procedure before redocking.

2.3. Molecular Docking and Validation

Docking was performed using the MOE Dock module to evaluate binding orientation, docking score, and intermolecular interactions of the selected phytochemicals with the PTP1B allosteric site. Because PDB 1T49 contains the experimentally resolved inhibitor 892, the docking region was defined from the position of this ligand rather than from an arbitrarily selected cavity [13],[19].

Ligand placement was conducted using the Triangle Matcher algorithm, followed by initial scoring with London dG and refinement/rescoring using GBVI/WSA dG, consistent with recent MOE docking workflows [17-18]. Final poses were ranked according to docking score and geometric plausibility. Because the pocket was defined directly from the co-crystallized ligand, explicit rectangular X, Y, and Z grid-box coordinates were not required [19].

Docking validation was performed by removing ligand 892 and redocking it into the same allosteric site using identical parameters. The predicted and crystallographic poses were superimposed, and the root-mean-square deviation (RMSD) was calculated [13-14]. An RMSD of <2.0 Å was considered acceptable [13-14]. The obtained RMSD of 1.388 Å indicated successful reproduction of the crystallographic pose and supported the reliability of the docking protocol for subsequent phytochemical screening. Protein–ligand interactions were further examined through hydrogen bonding, hydrophobic contacts, π-related interactions, and other relevant non-covalent contacts.

2.4. Drug-Likeness and ADMET Prediction

Drug-likeness was assessed using Lipinski's Rule of Five, including molecular weight, logP, hydrogen-bond donors, and hydrogen-bond acceptors, together with molecular flexibility and polarity descriptors such as rotatable bonds and topological polar surface area (TPSA) [20-22].

ADMET properties were predicted using the pkCSM web server, which has been applied in recent computational evaluations of phytochemicals [22-23]. The assessed parameters included intestinal absorption, Caco-2 permeability, P-glycoprotein interaction, volume of distribution, cytochrome P450 interactions, total clearance, AMES mutagenicity, and hepatotoxicity [22-23].

Docking results were interpreted together with drug-likeness and ADMET profiles rather than docking score alone. Compounds showing favorable PTP1B interactions together with comparatively acceptable physicochemical and predicted pharmacokinetic properties were considered higher-priority candidates for further experimental evaluation. As these pharmacokinetic and toxicity results were computational predictions, subsequent in vitro and in vivo validation remains necessary.

3. Results and Discussion

Gynura divaricata (L.) DC. is a medicinal plant rich in bioactive phenolic compounds and flavonoids with potential relevance to glucose regulation and insulin resistance [9],[20]. Recent phytochemical studies identified chlorogenic acid, 3,4-, 3,5-, and 4,5-dicaffeoylquinic acids, as well as kaempferol derivatives in *G. divaricata*, several of which showed α-glucosidase inhibitory activity and enhanced glucose uptake [9]. Related caffeoylquinic acid derivatives have also been reported to improve glucose metabolism by suppressing hepatic glucose production and enhancing insulin-signaling components such as INSR, IRS-1, and p-AKT [24], while flavonoids may exert multi-target antidiabetic effects through inhibition of enzymes including α-amylase, α-glucosidase, DPP-4, and PTP1B [25].

In addition, phenolic compounds such as chlorogenic, caffeic, and ferulic acids have been associated with antioxidant, anti-inflammatory, insulin-sensitizing, and glucose-regulating effects relevant to T2DM [26-27]. The phytochemicals selected for the present molecular docking analysis were based on compounds previously reported in *G. divaricata***,** as summarized in Table 1 [10].

Table 1. Bioactive compounds identified in *Gynura divaricata* leaves

No.	Compound	Reference
1	O-caffeoylquinic acid	[10]
2	5-O-feruloylquinic acid	[10]
3	Methyl 5-O-caffeoylquinate	[10]
4	Methyl 3,4-dicaffeoylquinate	[10]
5	Methyl 4,5-dicaffeoylquinate	[10]
6	Kaempferol	[10]
7	Quercetin	[10]
8	3,4-Dicaffeoylquinic acid	[10]
9	3,5-Dicaffeoylquinic acid	[10]
10	4,5-Dicaffeoylquinic acid	[10]

The compounds listed in Table 1 represent structurally related caffeoylquinic acid derivatives together with representative flavonoids reported in *G. divaricata* [10]. Caffeoylquinic acid derivatives are particularly relevant because differences in the number and position of caffeoyl groups may influence their biological and enzyme-inhibitory activities. Kaempferol and quercetin were included as structurally distinct flavonoids to provide a broader comparison of molecular interactions with PTP1B.

The compounds presented in Figures 2 and 3 include caffeoylquinic acid derivatives, dicaffeoylquinic acids, methylated caffeoylquinates, flavonoids, and sesquiterpenoid structures**.** Among these, caffeoylquinic acids and polyphenols have the strongest evidence for diabetes-related activity. *Gynura divaricata* contains chlorogenic acid, 3,4-diCQA, 3,5-diCQA, and 4,5-diCQA, several of which show α-glucosidase inhibition and enhanced glucose uptake [9]. Recent evidence also links phenolic acids and flavonoids from *G. divaricata* with glucose regulation, insulin sensitivity, antioxidant activity, and inflammatory control [20]. More broadly, caffeoylquinic acids and dietary polyphenols have been associated with improved glucose metabolism, reduced hyperglycemia, enhanced insulin sensitivity, and attenuation of oxidative stress [28-29].

Caffeoylquinic acid derivatives are particularly relevant because 5-CQA and dicaffeoylquinic acids can inhibit α-glucosidase and regulate glucose metabolism [9,28]. Related compounds have also been reported to increase glucose uptake, suppress hepatic glucose production, and improve insulin-signaling pathways [24]. Flavonoids may exert multi-target antidiabetic effects through modulation of glucose utilization and inhibition of enzymes such as PTP1B, α-glucosidase, α-amylase, and DPP-4 [25]. Their antioxidant activity is also relevant because oxidative stress contributes to insulin resistance and pancreatic β-cell dysfunction in T2DM [27],[29].

Sesquiterpenoids are also represented among the selected compounds, although their direct antidiabetic evidence remains less established than that of caffeoylquinic acids and flavonoids. A recent sesquiterpenoid-containing plant extract showed α-glucosidase and α-amylase inhibition, antioxidant activity, and glucose-lowering effects, but these effects were demonstrated for the extract rather than isolated sesquiterpenoids [30]. Additional studies directly involving *G. divaricata* have shown that its oligopeptides and polysaccharides can improve glycemic control and insulin sensitivity through AKT/FoxO1 and PI3K/Akt/GLUT4-related pathways [31-32]. Collectively, these findings support the chemical diversity and diabetes-related pharmacological potential of *G. divaricata* [20],[31-32].

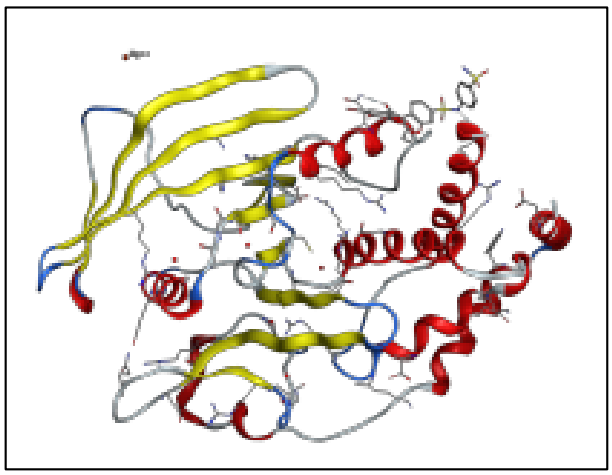

Figure 1. PDB protein: 1T49

Figure 1 shows the three-dimensional structure of human Protein Tyrosine Phosphatase 1B (PTP1B; PDB ID: 1T49), an X-ray crystal structure containing a co-crystallized allosteric inhibitor. This structure has been used in recent PTP1B docking studies for ligand-binding analysis and native-ligand redocking validation [13-14]. PDB 1T49 therefore provides a suitable structural model for investigating ligand interactions within the PTP1B allosteric region [12],[14].

PTP1B is an intracellular non-receptor protein tyrosine phosphatase that negatively regulates insulin signaling by dephosphorylating the insulin receptor and downstream IRS proteins [6],[33]. Its structure contains a conserved catalytic domain, including the WPD loop, together with regulatory allosteric regions [33]. In PDB 1T49, the co-crystallized inhibitor occupies an allosteric site located approximately 20 Å from the catalytic site [33]. These features support PTP1B as an important therapeutic target for T2DM and obesity [6],[33].

Molecular docking allows candidate compounds to be positioned within PTP1B binding regions to predict binding orientation, relative affinity, and key protein–ligand interactions [7],[13]. However, docking reflects predicted binding potential rather than direct therapeutic efficacy and is mainly useful for compound prioritization and mechanistic hypothesis generation [7]. Experimental studies nevertheless show that PTP1B inhibition can enhance GLUT4-related responses, improve insulin sensitivity, increase glucose uptake, and improve glucose tolerance in cellular and diabetic animal models [34–36].

Combining the PTP1B structural model with phytochemicals from *Gynura divaricata* therefore provides a framework for evaluating their predicted interactions with PTP1B and prioritizing promising candidates. Such ligand–target analysis can identify favorable binding modes and interaction patterns, but computational candidates still require biochemical, cellular, and *in vivo* validation [6-7],[34-36]. Although PTP1B remains a promising antidiabetic target, clinical translation is still limited by challenges involving selectivity, cellular permeability, bioavailability, and pharmacokinetic properties [6],[33].

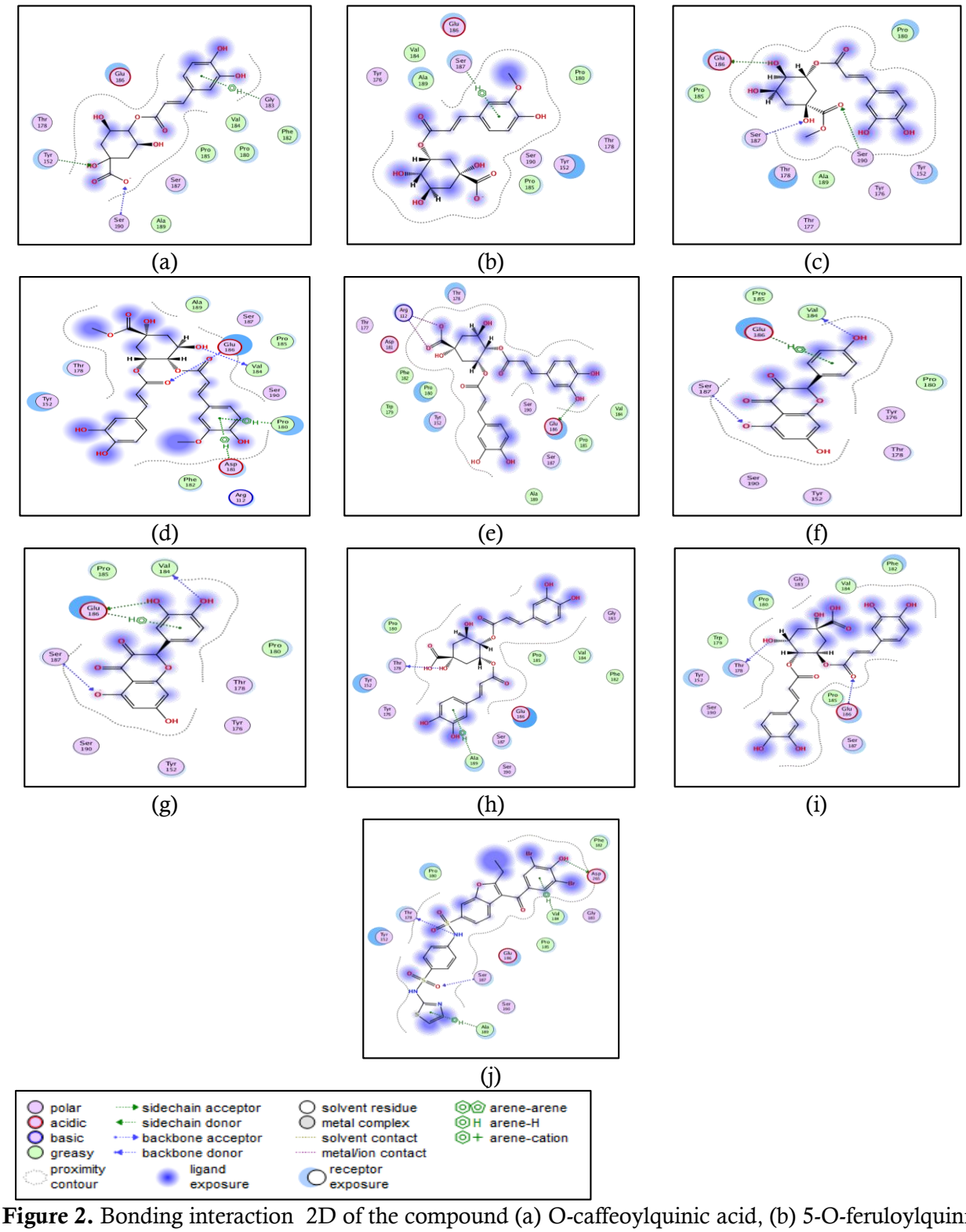

Figure 2. Bonding interaction 2D of the compound (a) O-caffeoylquinic acid, (b) 5-O-feruloylquinic acid, (c) Methyl 5-O-caffeoylquinate, (d) methyl 3,4-dicaffeoylquinate, (e) methyl 4,5-dicaffeoylquinate, (f) Kaempferol,(g) quercetin, (h) 3,4-dicaffeoylquinic acid, (i)3,5-dicaffeoylquinic acid, (j)4,5-dicaffeoylquinic acid

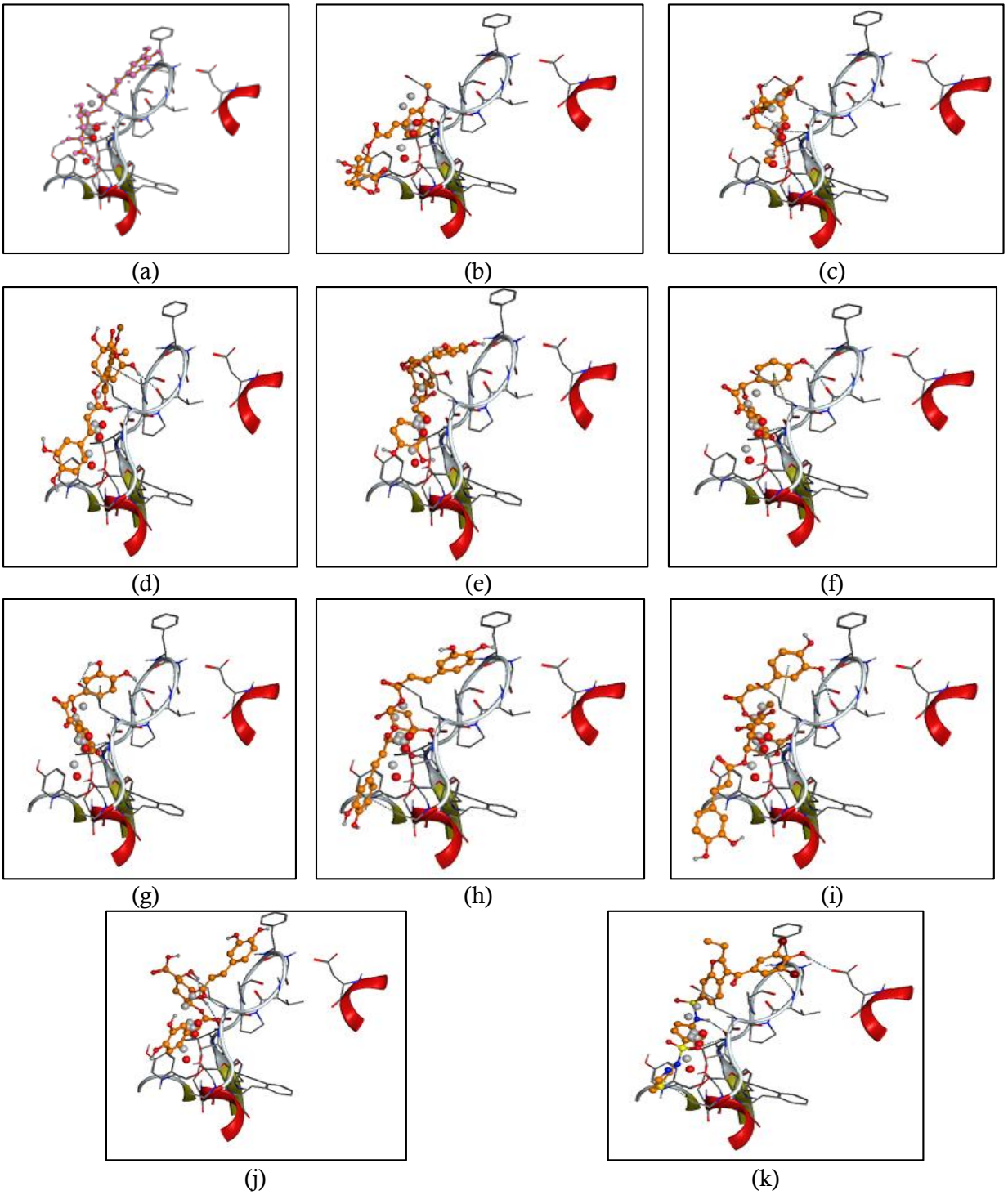

Figure 3. Bonding interaction 2D of the compound (a) O-caffeoylquinic acid, (b) 5-O-feruloylquinic acid, (c) Methyl 5-O-caffeoylquinate, (d) methyl 3,4-dicaffeoylquinate, (e) methyl 4,5-dicaffeoylquinate, (f) Kaempferol,(g) quercetin, (h) 3,4-dicaffeoylquinic acid, (i)3,5-dicaffeoylquinic acid, (j)4,5-dicaffeoylquinic acid and (k) protein target

Figure 2 illustrates two-dimensional interaction profiles of selected phytochemicals within diabetes-relevant protein binding sites. These maps show residue-level contacts such as hydrogen bonds, hydrophobic interactions, electrostatic contacts, and aromatic interactions**,** which help interpret predicted ligand recognition and binding orientation [37-40]. However, docking interactions represent predicted binding behavior rather than direct evidence of biological efficacy [37-39].

Hydrogen bonding and hydrophobic contacts help orient ligands within binding pockets, while π–π and π–cation interactions can provide additional stabilization [39-40]. Polyphenolic compounds with multiple hydroxyl groups and aromatic rings may offer several opportunities for hydrogen-bonding and aromatic interactions [37-38]. Residue-level analysis therefore complements docking scores by clarifying predicted ligand orientation and interaction patterns [37-40].

In *Gynura divaricata*, chlorogenic acid, 3,4-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid, and 4,5-dicaffeoylquinic acid have been identified as hypoglycemic constituents with α-glucosidase inhibitory activity and favorable docking interactions [9]. In another diabetes-focused study, 3,4-dicaffeoylquinic acid showed a DPP4 docking score of −7.7 kcal/mol, exceeding several reference inhibitors within the same protocol [41]. Related phenolics, including quercetin, caffeic acid, and ferulic acid, have also shown favorable predicted interactions with PTP1B [42].

For PTP1B, specific residue contacts should be interpreted directly from the present docking results because interaction patterns depend on the receptor structure and binding site examined [39-40]. Recent computational studies confirm that PTP1B and other T2DM-related proteins can accommodate ligands through combinations of hydrogen-bonding, hydrophobic, and aromatic interactions [37-40]. Thus, Figures 2 and 3 provide a structural basis for comparing the predicted binding patterns of selected *G. divaricata* phytochemicals and prioritizing candidates for further experimental validation [37-40].

Table 2. Docking scores of selected *Gynura divaricata* phytochemicals against PTP1B (PDB ID: 1T49)

No	Nama Senyawa	Docking Score (S) (kcal.mol^{-1})
1.	O-caffeoylquinic acid	-5.22150421
2.	5-O-feruloylquinic acid	-5.07844543
3.	Methyl 5-O-caffeoylquinate	-5.28116274
4.	methyl 3,4-dicaffeoylquinate	-5.98292971
5.	methyl 4,5-dicaffeoylquinate	-6.15764141
6.	Kaempferol	-4.56966972
7.	quercetin	-4.74145317
8.	3,4-dicaffeoylquinic acid	-6.38338232
9.	3,5-dicaffeoylquinic acid	-6.80571985
10.	4,5-dicaffeoylquinic acid	-6.07713366
11.	Tyrosine phosphatase 1B	-6.58695316

The selected *Gynura divaricata* phytochemicals showed docking scores ranging from −4.5697 to −6.8057 kcal/mol, indicating compound-dependent differences in predicted binding within the same docking protocol. More negative scores were interpreted as relatively more favorable predicted interactions, although docking energies do not directly represent experimental affinity or biological potency [7],[14],[43]. 3,5-Dicaffeoylquinic acid showed the most favorable score, followed by 3,4-dicaffeoylquinic acid and methyl 4,5-dicaffeoylquinate. Polyphenolic scaffolds can provide multiple hydrogen-bonding and hydrophobic interaction opportunities with PTP1B [41],[43].

Because PDB 1T49 represents an allosterically inhibited PTP1B conformation, interpretation of the docked compounds within this allosteric region is structurally appropriate [33,39]. Allosteric inhibition can interfere with conformational changes involving the WPD loop and associated α-helical

regions, thereby reducing PTP1B catalytic activity [33],[39]. Accordingly, docking-score differences should mainly be used to rank candidate ligands within the present computational setup.

Docking validation was performed by redocking the native ligand, with RMSD <2.0 Å considered acceptable for reproducing the crystallographic pose [14]. The obtained RMSD of 1.388 Å therefore supports the reliability of the docking setup. This criterion applies specifically to native-ligand redocking and should not be used as an acceptance threshold for phytochemical poses without experimental reference conformations [14].

Comparison with the reference ligand provides an additional benchmark when all compounds are evaluated using the same docking protocol [14],[41]. Phytochemicals with scores approaching the reference ligand may be prioritized computationally, but similar scores do not imply equivalent inhibitory or pharmacological potency. Recent PTP1B studies therefore strengthen docking predictions with molecular dynamics, binding free-energy calculations, enzyme assays, or biological validation [7],[14],[43].

Overall, the results suggest that *G. divaricata* caffeoylquinic acid derivatives can establish favorable predicted interactions with PTP1B and merit further investigation as candidate PTP1B ligands. This is biologically relevant because PTP1B negatively regulates insulin signaling, whereas its inhibition has been associated with improved glucose uptake, insulin sensitivity, and glycemic regulation [33-36]. However, these findings support computational prioritization rather than confirmed antidiabetic efficacy**,** and further biochemical, cellular, and *in vivo* validation remains necessary [7],[14],[36],[43].

Table 3. Ligand Redocking Interaction Profile with Protein 1T49

Ligand		Receptor				Interaction	Distance	E (kcal/mol)
N02	50	O	HIS	54	(A)	H-donor	2.99	-0.8
N02	50	O	HOH	545	(A)	H-donor	2.52	-0.8
O20	4	NZ	LYS	73	(A)	H-acceptor	2.90	-7.7
O20	4	O	HOH	450	(A)	H-acceptor	3.04	-3.4
O19	13	O	HOH	601	(A)	H-acceptor	3.15	-0.8
O01	34	CD	LYS	58	(A)	H-acceptor	3.45	-0.6
O01	34	O	HOH	533	(A)	H-acceptor	3.39	-1.0
O01	34	O	HOH	579	(A)	H-acceptor	2.74	-1.9
O02	35	N	LYS	58	(A)	H-acceptor	2.99	-1.7
O02	35	O	HOH	512	(A)	H-acceptor	3.16	-1.9
O02	35	O	HOH	533	(A)	H-acceptor	3.17	-1.7
O02	35	O	HOH	563	(A)	H-acceptor	3.22	-1.7
O02	35	O	HOH	619	(A)	H-acceptor	3.28	-1.6
O20	4	NZ	LYS	73	(A)	ionic	2.90	-5.2

The redocking analysis of the native ligand with PTP1B (PDB ID: 1T49) was used to assess reproduction of the crystallographic pose and characterize ligand–protein interactions. Recent PTP1B studies have similarly used PDB 1T49 and native-ligand redocking for docking validation and allosteric binding analysis [14]. Protein–ligand recognition is generally mediated by hydrogen-bonding, electrostatic, hydrophobic, and aromatic interactions [33],[44].

In the present model, the ligand formed several non-covalent interactions, particularly hydrogen-bonding and electrostatic contacts. These interactions are consistent with the structural characteristics of PTP1B, whose catalytic and regulatory regions contain polar, charged, and hydrophobic residues involved in molecular recognition [33]. His54 and Lys73 were identified as ligand-contacting residues, and similar involvement of these residues has been reported in recent PTP1B interaction studies [45].

The observed hydrogen-bond distances of approximately 2.7–3.5 Å are compatible with plausible polar contacts, although interaction strength also depends on donor–acceptor geometry and the local environment [44]. The ionic interaction involving Lys73 should therefore be regarded as a specific feature of the present docking model rather than a universally conserved PTP1B interaction. Together, these contacts provide a structural basis for the predicted ligand orientation within the binding region [33],[44-45].

Water-mediated interactions may further influence PTP1B complexes when explicit solvent is included. Recent molecular-dynamics studies have identified water bridges involving residues such as Lys36, Asp48, Ser50, Asp29, and Gln262 in PTP1B–polyphenol complexes [46]. However, if crystallographic water molecules were removed during receptor preparation, such interactions should not be interpreted as direct results of the present redocking analysis.

Overall, the redocking profile supports the ability of the docking protocol to reproduce a plausible ligand orientation and identify relevant residue-level contacts within PTP1B [14]. The observed hydrogen-bonding and electrostatic interactions are consistent with current structural understanding of PTP1B recognition [33],[44]. Contacts involving His54 and Lys73 should nevertheless be regarded primarily as findings of the present computational model [45].

Tabel 4. List of compounds based on ADMET parameters from Gynura divaricata leaves

NO	Compound	ABSORPTION						DISTRIBUTION		METABOLISM					EXCRETION		TOXICITY			
		GI	Water solubility (log mol/L)	$CaCo_2$ permeability (log Papp in 10^{-6} cm/s)	Intestinal absorption (% Absorbed)	Pgp Substrate	Pgp Inhibitor	VDss (human) (log L/kg)	Fraction unbound (human) (Fu)	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor	Renal OCT2 (Substrate)	Total Clearance	Max. tolerated dose (log mg/kg/day)	Oral Rat Acute Toxicity (LD_{50}) (mol/kg)	Hepatotoxicity	AMES toxicity
1	O-caffeoylquinic acid	High	-3.914	-0.597	34.4	Yes	Yes	-1.679	0.282	No	No	No	No	No	No	0.106	-0,85	1.568	No	No
2	5-O-feruloylquinic acid		-2.537	-0.469	35.685	Yes	No	-1.317	0.528	No	No	No	No	No	No	0.403	0.503	1.567	No	No
3	Methyl 5-O-caffeoylquinate		-2.775	-0.442	52.609	Yes	No	no	0.517	No	No	No	No	No	No	0.193	0.634	1.615	No	Yes
4	methyl 3,4-dicaffeoylquinate		-3.236	0.08	56.402	Yes	Yes	0.69	0.046	No	No	No	No	No	No	0.111	0.064	2.475	No	No
5	methyl 4,5-dicaffeoylquinate		-2.955	-1.203	29.037	Yes	No	0.011	0.381	No	No	No	No	No	No	-62.938	0.438	2.482	No	No
6	Kaempferol		-3.04	0.032	74.29	Yes	No	1.274	0.178	No	No	No	No	No	No	0.477	0.531	2.449	No	No
7	quercetin		-2.925	-0.229	77.207	Yes	No	1.559	1.559	No	No	No	No	No	No	0.407	0.499	2.471	No	No
8	3,4-dicaffeoylquinic acid		-2.955	-1.203	29.037	Yes	No	1.633	0.294	No	No	No	No	No	No	-0.042	0.393	2.626	No	No
9	3,5-dicaffeoylquinic acid		-2.897	-1.207	17.004	Yes	No	1.53	0.232	No	No	No	No	No	No	0.076	0.368	2.492	No	No
10	4,5-dicaffeoylquinic acid		-2.955	-1.203	29.037	Yes	No	1.633	0.294	No	No	No	No	No	No	-0.042	0.393	2.626	No	No
11	Tyrosine phosphatase 1B		-3.503	0.261	89.714	Yes	Yes	-1.165	0.133	No	Yes	Yes	No	Yes	No	-0.39	0.355	3.087	Yes	No

The ADMET evaluation of selected *Gynura divaricata* phytochemicals showed compound-dependent pharmacokinetic and toxicity profiles, with several compounds displaying potentially favorable predicted characteristics. Early ADMET assessment is important because inadequate absorption, distribution, metabolism, excretion, or toxicity profiles remain major causes of drug-candidate attrition [47]. These results should therefore be interpreted as preliminary predictions for compound prioritization rather than experimental evidence of efficacy or safety [47].

Predicted intestinal absorption and Caco-2 permeability were used to estimate the potential intestinal transport of the compounds. Favorable values for both parameters may indicate better predicted absorption, although oral bioavailability is also influenced by metabolism, efflux, and other physiological factors [48]. Thus, these parameters provide supportive but not definitive evidence of systemic exposure [48].

Several compounds were predicted to interact with P-glycoprotein (P-gp), an efflux transporter that can influence intestinal absorption and drug disposition [49]. Lack of predicted P-gp inhibition may reduce the likelihood of transporter-mediated drug interactions, although P-gp substrates may still undergo significant efflux [49]. Fraction unbound was also evaluated because plasma-protein binding affects tissue distribution, clearance, and systemic exposure [50].

Predicted blood–brain barrier (BBB) permeability was interpreted as an indicator of potential CNS exposure rather than overall safety. Limited BBB penetration may be appropriate for compounds intended to act mainly on peripheral metabolic targets, but it should not itself be considered evidence of safety [51]. Overall, the ADMET results provide a preliminary basis for prioritizing *G. divaricata* phytochemicals for further in vitro and in vivo pharmacokinetic and toxicity evaluation [47-51].

Table 5. Physicochemical Properties of Compounds Based on Lipinski's and Veber's Rules

No	Compound	Lipinski Ro5				Veber		Bioavailability Score
		H-Donor (<5)	H-Acceptor (<10)	Log P (<5)	Mw (g/mol) (<500)	Rotatable Bonds (≤ 10)	PSA Å (<140)	
1	O-caffeoylquinic acid	6	12	4,15	530.48	10	200	0.11
2	5-O-feruloylquinic acid	5	9	1.76	368	6	153	0.11
3	Methyl 5-O-caffeoylquinate	5	9	1.64	368.34	6	153.75	0.55
4	methyl 3,4-dicaffeoylquinate	5	9	1.64	368.34	6	153.75	0.55
5	methyl 4,5-dicaffeoylquinate	5	9	1.64	368.34	6	153.75	0.55
6	Kaempferol	4	6	1.70	286.24	1	111.13	0.55
7	quercetin	5	7	1.63	302.24	1	131.36	0.55
8	3,4-dicaffeoylquinic acid	7	12	0.48	516	9	211.28	0.11
9	3,5-dicaffeoylquinic acid	7	12	0.48	516	9	211.28	0.11
10	4,5-dicaffeoylquinic acid	7	12	0.48	516	9	211.28	0.11
11	Tyrosine phosphatase 1B	3	8	2.08	741	9	200	0.11

The redocking result shows the superimposition of the predicted native-ligand pose with its original co-crystallized conformation in PTP1B (PDB ID: 1T49), a well-established therapeutic target for T2DM and obesity because of its negative regulatory role in insulin signaling [33],[52]. The 1T49 structure has been used in recent PTP1B studies for allosteric ligand-binding analysis and redocking validation [13].

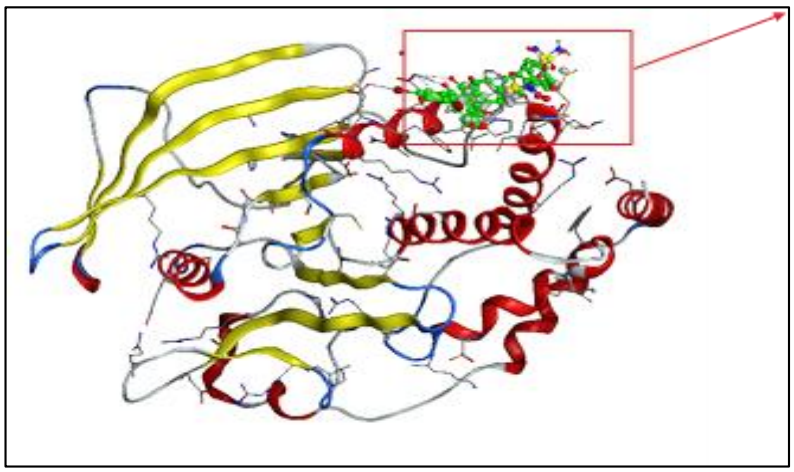

Figure 4. Redocking

In structure-based drug discovery, redocking assesses whether a docking protocol can reproduce the experimentally observed pose of a co-crystallized ligand by superimposing the predicted and crystallographic conformations and calculating their root-mean-square deviation (RMSD) [13],[53].

An RMSD below approximately 2.0 Å is generally considered acceptable evidence of successful pose recovery, although self-docking alone does not guarantee accurate prediction for new ligands and may be complemented by cross-docking, structural plausibility assessment, benchmarking, or experimental validation [13],[53]. Thus, successful redocking of the native ligand supports the ability of the present protocol to reproduce the 1T49 reference binding pose and provides a suitable basis for subsequent phytochemical docking analysis [13],[53].

Tabel 6. Comparison of crystal ligand and docking

Compounds	S (Kcal/Mol)	Rmsd	H Bond	Metal Bond	Ionic Bond	Binding Factor
Co-crystal ligand	-4.7077	1.3996	HOH360, HOH324	-	-	-
Re-docking ligand	-5.6298	1.388	**GLU200**, **GLU276**, **ARG39**	-	**ASP41, ASP41**	8

Docking validation was performed by redocking the native co-crystallized ligand into the PTP1B allosteric site (PDB ID: 1T49), consistent with recent PTP1B studies using 1T49 for allosteric docking validation [13-14]. The redocked pose produced an RMSD of 1.388 Å, below the commonly accepted ~2.0 Å threshold for successful pose recovery [13],[53]. This value represents protocol validation and should be distinguished from RMSD values of test-ligand poses or those obtained during molecular dynamics, which reflect different computational properties [53].

The close superimposition in Figure 4 indicates successful geometric recovery of the native ligand pose, although low RMSD does not necessarily guarantee full recovery of hydrogen-bonding, hydrophobic, ionic, and π-interaction patterns [55]. Recent PTP1B studies report stabilizing aromatic interactions involving residues such as Phe196 and Phe280 [54]. Thus, the validated protocol provides a suitable basis for subsequent phytochemical screening, while docking-score rankings should be interpreted as relative computational prioritization rather than experimental binding affinity, with further validation by molecular dynamics, free-energy calculations, or biological assays recommended [13],[53-55].

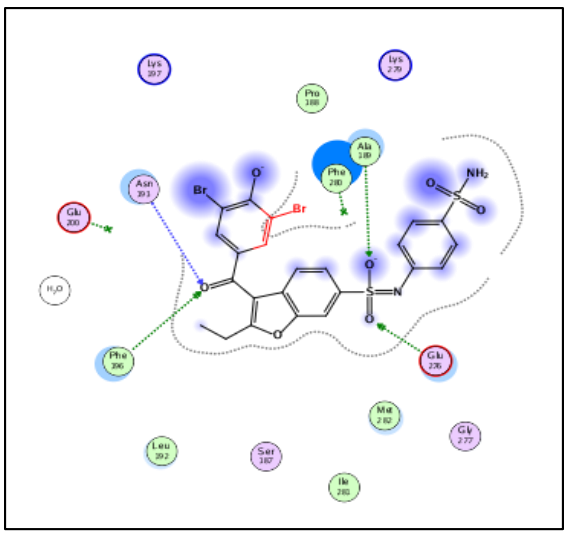

Figure 5. Interaction native ligan 1T49

Figure 5 shows the two-dimensional interaction profiles of the native ligand and its redocked pose within the allosteric binding site of PTP1B (PDB ID: 1T49), a structure widely used for allosteric docking and redocking validation [13-14]. The 1T49 allosteric region lies approximately 20 Å from the catalytic site and includes residues such as Leu192, Asn193, Phe196, Glu276, Lys279, and Phe280, which contribute to ligand recognition through polar, hydrophobic, and aromatic interactions [13],[33]. In particular, Phe196 and Phe280 have been reported to form stabilizing π–π interactions with allosteric PTP1B inhibitors [54]. Thus, comparison of the native and redocked interaction profiles provides complementary evidence of pose recovery and preservation of relevant allosteric-site contacts [13-14][54].

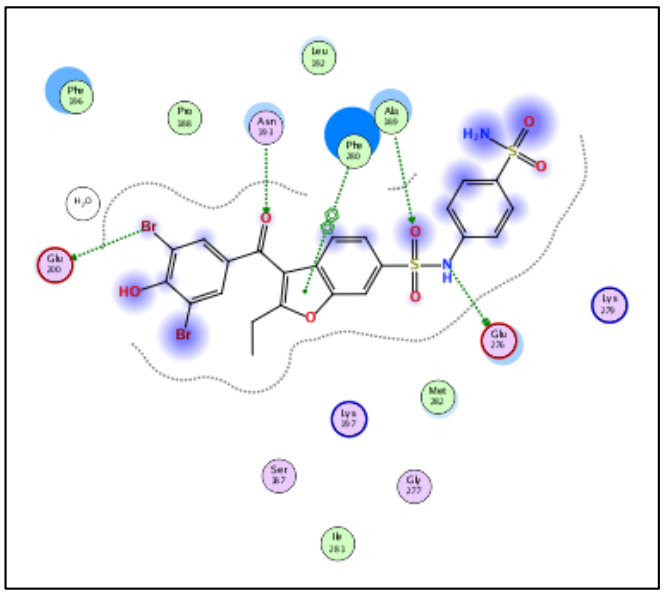

Figure 6. Visualisasi ligan redocking

The redocking result in Figure 6 shows that the ligand is well accommodated within the PTP1B allosteric binding pocket, where residues such as Leu192, Asn193, Phe196, Glu276, Lys279, and Phe280 contribute to ligand recognition and stabilization through polar, hydrophobic, and aromatic interactions [13-14],[39]. In particular, Phe196 and Phe280 are repeatedly reported as important aromatic residues involved in π-mediated interactions that support allosteric ligand binding [39,54]. The two-dimensional interaction profile therefore provides complementary structural information on the non-covalent contacts that support the redocked pose [13-14,][54]. These interactions should, however, be interpreted as computational evidence of binding-mode plausibility rather than direct evidence of experimental binding affinity [13],[54].

4. Conclusion

This study demonstrates that the phytochemical constituents of *Gynura divaricata* possess strong potential as natural inhibitors of Protein Tyrosine Phosphatase 1B (PTP1B), a key enzyme associated with insulin resistance and Type 2 Diabetes Mellitus. Among the eleven evaluated compounds, several caffeoylquinic acid derivatives, particularly 3,5-dicaffeoylquinic acid and methyl 3,4,5-tricaffeoylquinic acid, showed the most favorable docking scores, which were comparable to the standard control inhibitor. These compounds exhibited stable molecular interactions through multiple hydrogen bonds and ionic forces, primarily involving Lys73 and His residues, contributing to strong affinity and stable complex formation within the protein's active site.

ADMET profiling further supported their pharmacological relevance by indicating acceptable absorption, metabolism, and low predicted toxicity, suggesting good drug-like behavior. Redocking validation confirmed the reliability of the docking protocol, with RMSD values falling within acceptable ranges, ensuring that the predicted interactions were structurally consistent. Overall, the findings provide strong computational evidence that *Gynura divaricata* contains bioactive molecules with promising antidiabetic potential through PTP1B inhibition. These results warrant further in vitro and in vivo investigations to confirm their therapeutic efficacy and to explore their development as natural antidiabetic agents.

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