Journal of Tropical Biodiversity and Biotechnology
Volume 08, Issue 03 (2023): jtbb83124
DOI: 10.22146/jtbb.83124

Research Article

In silico Screening of Potential Antidiabetic Phenolic Compounds from Banana (*Musa* spp.) Peel Against PTP1B Protein

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Keywords:
antidiabetic
banana peel
diabetes mellitus
in silico
phenolic compound
PTP1B
Submitted:
15 March 2023
Accepted:
11 July 2023
Published:
25 October 2023
Editor:
Ardaning Nuriliani

ABSTRACT

Type 2 diabetes mellitus (T2DM) is a global problem with increasing prevalence. The current treatments have made an immense progress with some side effects, such as drug resistance, acute kidney toxicity, and increased risk of heart attack. Banana (*Musa* spp.) peel comprises 40% of banana fruit contains high phenolic compounds whilst some studies have suggested a correlation between phenolic compounds and antidiabetic activity. One of the novel protein targets that has been identified as a potential anti-diabetic treatment is PTP1B (PDB ID:2NT7). Therefore, this study aimed to screen the potential PTP1B inhibitor for antidiabetic treatment from phenolic compounds in banana peel. QSAR, molecular docking, ADME-Tox, and molecular dynamics analysis were deployed to examine forty-three phenolic compounds in banana peel. Eighteen ligands were screened by QSAR analysis and eight of them had a lower binding energy than the standard (ertiprotafib) in molecular docking, with urolithin A and chrysin were the lowest. Both passed Lipinski's rule of five, had a good intestinal absorption, and no blood-brain barrier penetration, however, their mutagenicity, carcinogenicity, and irritation to the skin and eyes were still in questions. Molecular dynamics analysis found both of them were in a stable conformation with PTP1B. This study suggested a potential of urolithin A and chrysin as PTP1B inhibitor for antidiabetic treatment. Additionally, further experimentation is required to validate this finding.

INTRODUCTION

Type 2 Diabetes mellitus (T2DM) is a metabolic disease characterized by elevation of blood glucose level caused by a complex pathophysiology (Galicia-Garcia et al. 2020). Diabetes affects 415 million people globally and T2DM encompasses 90% of the patients (Chatterjee et al. 2017). Pathophysiology of T2DM includes initial insulin resistance which is compensated by an increase in insulin secretion to maintain glucose homeostasis, yet over time failure in β-cell occurs and insulin secretion is diminished, causing hyperglycemia (Goyal & Jialal 2020).

Current treatment of T2DM is focused on disease management, including diet, exercise, and blood glucose monitoring as well as pharmacological treatment (Goyal & Jialal 2020). In general, common targets for

antidiabetic drugs are categorized into insulin secretagogues, mimickers, and sensitizer, as well as starch and sugar blockers (Kanwal et al. 2022). Food and Drugs Administrative (FDA) has approved 59 antidiabetic drugs (36 mono- and combinatorial therapies) (Dahlén et al. 2022). However, this pharmacological treatment poses adverse effects, including drug resistance, acute kidney toxicity, and increased risk of heart attack (Salehi et al. 2019). Therefore, it is necessary to find a new therapeutic agent with less adverse effects, yet with better efficacy as a means to manage T2DM.

Approximately a hundred of new antidiabetic drugs are being developed in more than three hundreds clinical trials (Dahlén et al. 2022). Interestingly, 40% of these new drugs target novel therapeutic targets. One of the promising target for the antidiabetic treatment is Protein Tyrosine Phosphatase 1B (PTP1B) (Eleftheriou et al. 2019). PTP1B is known as a negative regulator in the insulin signalling pathway, in which it dephosphorylates insulin receptor and its substrate that eventually desensitize insulin action (Tautz et al. 2013; Eleftheriou et al. 2019; Liu et al. 2022). Interestingly, in a study of PTP1B knock-out mice exhibited better glucose control and insulin sensitivity (Haj et al. 2005). Therefore, its inhibition is thought to be a promising target for T2DM.

With a production of 120 tonnes annually, banana is the most produced fruit in the world, with India as the biggest producers, followed by China, Indonesia, and Uganda (Food and Agriculture Organization of the United Nations 2022). Comprising 40% of the fruit, banana peel is a major fruit waste (Sharma et al. 2016). This results in an enormous volume of waste being sent to the landfill or incinerator, which, if handled improperly, would later result in the emission of greenhouse gases and the generation of harmful incomplete combustion materials, among other environmental problems. On the other hand, banana peel is a good source of phytochemicals, including phenolic compounds (Acevedo et al. 2021). Therefore, it is important to identify alternate uses for banana peel.

In recent years, there has been growing interest in phenolic compounds due to their abundance in plants as secondary metabolites and their potential health-promoting roles, including as antioxidants, anticancer agents, anti-diabetic agents, inhibitors of adipogenesis, regulators of blood pressure, and suppressors of inflammatory genes (Gutiérrez-Grijalva et al. 2016). Specifically, the anti-diabetic effects of phenolic compounds have been extensively studied in animal and in limited human models, showing a decrease in blood glucose and improvement of insulin secretion and sensitivity (Aryaeian et al. 2017; Naz et al. 2019). Research has also shown that phenolic extracts from certain plants, such as persimmon, finger millet, raspberry, cumin, and fig, exhibit antidiabetic properties by inhibiting enzymes such as α-amylase and α-glucosidase (Asgar 2013; Wojdyło et al. 2016; Praparatana et al. 2022). *In silico* studies have also shown that phenolic compounds in anthocyanins, flavanols, flavonoids, and proanthocyanidins have the highest potential for antidiabetic effects (Asgar 2013; Damián-Medina et al. 2020; Mudunuri et al. 2022). Specifically, few studies have also predicted the potential inhibition of PTP1B by some phenolic compounds (Damián-Medina et al. 2020; Rath et al. 2022). However, despite extensive research, there is still a lack of understanding about the antidiabetic potential of phenolic compounds from banana peel.

Therefore, this study aimed to screen potential phenolic compounds in banana peel on antidiabetic property against PTP1B protein using an *in silico* approach, including Quantitative Structure-Activity Analysis (QSAR), molecular docking and visualization, Absorption, Distribution,

Metabolism, Excretion, and Toxicity (ADME-Tox) prediction, and molecular dynamics simulation, which further can be used as a new candidate for diabetes treatment.

MATERIALS AND METHODS

Materials

Structures of forty-three phenolic compounds in banana peel and ertiprotafib (CID: 157049) as standard were retrieved from PubChem Database (https://pubchem.ncbi.nlm.nih.gov/) (Kim et al. 2021). PTP1B protein (PDB ID: 2NT7) was retrieved from Protein Data Bank (https://www.rcsb.org/) (Burley et al. 2021).

Methods

The workflow of this study includes structure retrieval and preparation, QSAR analysis, molecular docking and visualization, ADME-Tox prediction, and molecular dynamics simulation (Wijaya et al. 2021; Wisnumurti et al. 2022).

Structure Retrieval and Preparation

Phenolic compounds in banana peel were reviewed from literature (Aboul-Enein et al. 2016; Suleria et al. 2020; Bashmil et al. 2021), retrieved from PubChem Database, and used as ligands. Ertiprotafib, which is a PTP1B inhibitor that has passed phase II clinical trial was used as standard in this study and its structure was retrieved from PubChem Database as well (Liu et al. 2022). The ligands and standard were retrieved in SMILES (simplified molecular input line entry system) format for QSAR and ADME-Tox analysis, and .sdf format for molecular docking and molecular dynamics simulation (Aurora et al. 2022). Their energy was minimized prior to docking and converted to .pdbqt format using OpenBabel wizard in PyRx (Wicaksono et al. 2022).

Structure of PTP1B protein (PDB ID: 2NT7) was retrieved from Protein Data Bank (https://www.rcsb.org/) (Burley et al. 2021). PyMol was used to remove unnecessary residues (water and innate ligand) attached to the retrieved structure.

QSAR Analysis

The QSAR analysis was used to predict and initially screen the potential ligand based on the relationship between chemical structure and biological activity with known compounds. PASS online (http://www.way2drug.com/passonline/) is an online software used for QSAR analysis (Filimonov et al. 2014). SMILES of the ligands were inputted into the server and the results were shown in probability of activity (Pa) and probability of inactivity (Pi). Having Pa > Pi suggests the activity to be possible (Hussain et al. 2016).

Molecular Docking Validation

Re-docking was performed before the study to validate the procedure. A native inhibitor (PDB Chem ID: 902) was removed from crystalised structure of PTP1B (PDB ID: 2NT7) and re-docked against the protein using Vina wizard in PyRx. The re-docking followed the same protocol to ensure that the docking protocol is capable to precisely dock the ligands into the protein, reflected by the less deviation of the re-docked native ligand from the original co-crystalized position calculated in RMSD (root-mean-square deviation) value using Discovery Studio. RMSD of <2 Å is regarded sufficient to validate the docking protocol (Pratama et al. 2021).

Molecular Docking and Visualization

Molecular docking was performed to the selected ligands towards PTP1B using Autodock Vina wizard (Eberhardt et al. 2021) in PyRx (Dallakyan & Olson 2015). In addition, a standard was docked towards PTP1B to compare and determine the similarity of the interaction between the ligands and standard. The results of molecular docking were in the form of binding energy scores (kcal/mol) with a more negative value means a higher affinity. Docking grid was set to the whole protein, with the centre of X:44.2, Y:16.8, and Z:15.1, and dimensions of X:62.9, Y:53.3, and Z:42.7. The interaction between amino acid residues of PTP1B and ligands were illustrated by 2D visualization using BIOVIA Discovery Studio (BIOVIA Systèmes Dassault 2019).

ADME-Tox Prediction

The ADME-Tox analysis was used to predict the pharmacokinetics and toxicity of the ligands when used as drugs. ADMETlab 2.0, a webserver ADME-Tox software which is able to predict ADME-related, toxicity, and medicinal properties, was used for this analysis (Xiong et al. 2021). SMILES of the selected ligands were inputted into the server and several parameters were analysed , including Lipinski's Rule of Five, human intestinal absorption (HIA), blood-brain barrier (BBB), Ames toxicity, carcinogenicity, skin sensitization, eye irritation, LC_{50} of fathead minnow and *Daphnia magna*.

Molecular Dynamics Simulation

The selected ligands in the complexes with PTP1B were subjected to molecular dynamics simulation to analyse conformational changes and stability of the complex in a dynamic model. Online server CABS-Flex 2.0 is a webserver to conduct a molecular dynamics simulation in a low computational cost yet with an accurate result used in this study (Kuriata et al. 2018). Selected ligands-protein complexes were subjected to this analysis and inputted into the server in .pdb format and the other parameters were left default.

RESULTS AND DISCUSSION

Quantitative Structure-Activity Relationship Analysis

Initially, forty-three phenolic compounds from banana peel were reviewed from the literature (Table 1). All of them were subjected to QSAR analysis using PASS online for antidiabetic and PTP1B inhibitory activity. Antidiabetic activity refers to the ability to reduce blood glucose level which occurs through several means, including insulin secretion, as well as promoting and inhibiting diabetes-related protein (Kanwal et al. 2022). In order to narrow down the selection, PTP1B inhibitory activity was also analysed.

Pa is the probability of being active while, contrary, Pi is the probability of being inactive, therefore, by default, only Pa > Pi is considered possible for a biological activity (Filimonov et al. 2014). A total of 18 phenolic compounds were selected based on the parameter above (Table 2). In regards to the Pa, a threshold of Pa > 0.7 indicates a highly significant activity, Pa = 0.3 – 0.7 indicates moderate activity, while Pa < 0.3 indicates a low activity (Parikesit & Nurdiansyah 2021). However, low Pa value does not certainly mean that they have low activity, because studies of the similar compounds are limited, hence the low probability (Kusuma et al. 2022). In fact, if it would be experimentally confirmed, the compound might happen to be a new structurally active compound (Hussain et al. 2016). Therefore, they were subjected to further analysis in molecular docking.

Molecular Docking Validation

Using the same docking protocol, the native ligand was re-docked against the protein to retrieve the predicted binding conformation. Subsequently, the re-docked ligand was compared to its co-crystalised struc-

Table 1. Phenolic compounds from banana peel.

Compounds	Class	Banana Species
Caffeic acid	Phenolic Acids	MP
Chlorogenic acid	Phenolic Acids	MAC
Ferulic acid		MAC
Gallic acid		MAC
Protocatechuic acid 4-O-glucoside	Hydroxybenzoic Acid	MAC
2-Hydroxybenzoic acid		MAC
3,4-O-Dimethylgallic acid		MAL
Caffeoyl glucose	Hydroxycinnamic Acid	MAC
Cinnamic acid		MP, MAC
m-coumaric acid		MAC
3-Hydroxyphenylpropionic acid	Hydroxyphenylpropanoic Acids	MAC
p-Coumaroyl glycolic acid		MAC, MAD, MAL, MAR, MP,
3,4-Dihydroxyphenylacetic acid	Hydroxyphenylacetic Acids	MAC, MAR
Urolithin A	Hydroxycoumarins	MAC
Scopoletin		MP
Umbelliferone		MAM
Cyanidin 3,5-O-diglucoside	Anthocyanins	MAR
Delphinidin 3-O-(6”-acetyl-galactoside)		MP, MAC, MAM
Malvidin 3-O-(6”-acetyl-glucoside)		MAR
Chrysin	Flavones	MP
Gardenin B		MAC
Cirsilineol		MAC
Chrysoeriol 7-O-glucoside		MAC
6-Hydroxyluteolin 7-rhamnoside		MAC
Hesperetin 3'-O-glucuronide	Flavanones	MAC
Naringenin		MAC
Neoeriocitrin		MAR
3-Methoxysinensetin	Flavonols	MAC
Isorhamnetin 3-O-glucoside 7-O-rhamnoside		MAC
Myricetin 3-O-galactoside		MAC
Myricetin 3-O-rhamnoside		MAC
Myricetin 3-O-rutinoside		MAC
Patuletin 3-O-glucosyl-(1->6)- [apiosyl(1->2)]-glucoside		MAR
Quercetin 3-O-xylosyl-glucuronide		MAC
Rutin		MAC
5,6,7,3',4'-Pentahydroxyisoflavone	Isoflavonoids	MAC
Isoquercitrin		MAC
4-Hydroxybenzaldehyde	Hydroxybenzaldehydes	MAC
Demethoxycurcumin	Curcuminoids	MAC
Isopimpinellin	Furanocoumarins	MAC
Carnosic acid	Phenolic Terpenes	MAC
Schisantherin A	Lignans	MAC
Salvianolic acid B	Other Polyphenols	MAC

Note: MP: *Musa paradisiaca*, MAC: *Musa acuminata* Canvendish, MAD: *Musa acuminata* Ducasse, MAL: *Musa acuminata* Ladyfinger, MAR: *Musa acuminata* Red Dacca, MAM: *Musa acuminata* Monkey. Adapted from Suleria et al. (2020), Bashmil et al. (2021), and Aboul-Enein et al. (2016).

Table 2. PASS Online Prediction Results.

Compounds	Antidiabetic		PTP1B Inhibitor	
	Pa	Pi	Pa	Pi
Ertiprotafib (standard)	0,925	0,004	0,700	0.002
Caffeic acid	0.385	0.048	0,188	0,014
Ferulic acid	0,274	0,098	0,228	0,009
Gallic acid	0,317	0,073	0,167	0,018
3,4-O-Dimethylgallic acid	0,510	0,022	0,159	0,019
p-Coumaroyl glycolic acid	0,443	0,033	0,278	0,006
3,4-Dihydroxyphenylacetic acid	0,510	0,022	0,159	0,019
Urolithin A	0,251	0,074	0,171	0,017
Scopoletin	0,172	0,031	0,071	0,062
Umbelliferone	0,241	0,008	0,106	0,039
Chrysin	0,317	0,031	0,174	0,016
Gardenin B	0,326	0,027	0,106	0,039
Cirsilineol	0,300	0,039	0,116	0,033
Hesperetin 3'-O-glucuronide	0,504	0,023	0,071	0,062
Naringenin	0,229	0,132	0,171	0,017
3-Methoxysinensetin	0,381	0,015	0,139	0,024
5,6,7,3',4'-Pentahydroxyisoflavone	0,305	0,037	0,086	0,051
Carnosic acid	0,223	0,050	0,132	0,026
Salvianolic acid B	0,572	0,015	0,149	0,022

ture by measuring the RMSD value. RMSD value between re-docked ligand and co-crystalized ligand was 1.254 Å (Figure 1A). Both results showed the same orientation with only a slight shifted position around the rotatable bond. The re-docked ligand showed a binding energy value of -9.3 kcal/mol and the interactions with amino acid residues is depicted in Figure 1B.

Molecular Docking and Visualisation

Molecular docking analysis was carried out to predict both the structural conformation of the ligands necessary to bind with PTP1B as well as the

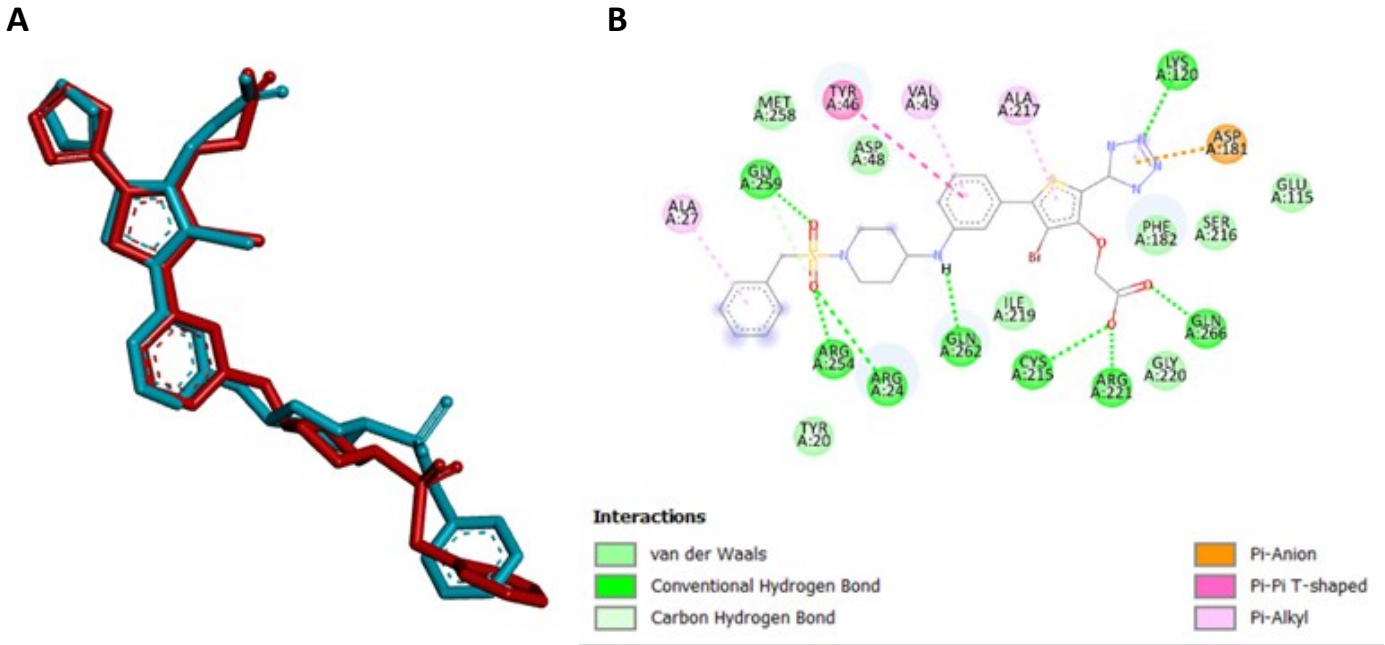

Figure 1. Molecular docking validation. Superimposed re-docked ligand (blue) to co-crystallized ligand (red) (A). Interactions of re-docked ligand with amino acid residues (B).

strength of binding reflected by their binding energy. Binding energy is integral to the inhibitory effect since the inhibition of the biological activity is the results of ligand binding to the protein target (Lopina 2017). The interaction between ligands and PTP1B could be analysed based on the binding energy. The lower the binding energy, the more stable is the ligands since they require smaller energy to bind with the protein binding site.

Binding energy of the ligands with PTP1B is depicted in Table 3. It showed that 8 ligands had binding energy lower than the standard (-7.4 kcal.mol). In that regard, it implied that they could form a stronger, more efficient complexes with PTP1B. The lead ligands which inhibited PTP1B, therefore, are urolithin A and chrysin, since both of them had a better binding energy score than the standard and other ligands, with a binding energy of -8.8 kcal/mol.

Discovery Studio used for the visualization is not only able to predict the favourable bonds, namely charged, halogen, hydrophobic, and hydrogen bonds, but also the unfavourable bonds, including steric bumps, charge repulsion, acceptor-acceptor and donor-donor clashes (Biovia 2019). Favorable bonds are responsible for increasing binding affinity due to intermolecular attraction, including hydrogen bonds, covalent bond, Van der Waals interaction, electrostatic force, and coordination bond (Chen & Krugan 2009). On the other hand, unfavourable bonds dictate the repulsion in the ligand-protein binding, hence lowering the binding affinity. Formed favourable and unfavourable bonds were used to corelate the binding affinity scores and how they achieved those. Additionally, presence of unfavourable bonds also affects the stability of ligand-protein complex due to repulsion (Dhorajiwala et al. 2019).

Figure 2 depicts the interactions between ligands and amino acid residues in PTP1B. Urolithin A showed interactions with residue Tyr46, Val49, Phe182, Ala217, and Arg221, while chrysin with Val49, Ala217,

Table 3. Molecular Docking Results.

Compounds	Class	Binding Energy (kcal/mol)
Ertiprotafib (standard)	-	-7.4
Caffeic acid	Phenolic acids	-6.7
Ferulic acid		-5.5
Gallic acid		-6.2
3,4-O-Dimethylgallic acid	Hydroxybenzoic acids	-6.5
p-Coumaroyl glycolic acid	Hydroxyphenyl-propanoic acids	-6.9
3,4-Dihydroxyphenylacetic acid	Hydroxyphenyl-acetic acids	-6.5
Urolithin A*	Hydroxycoumarins	-8.8
Scopoletin		-7.2
Umbelliferone		-6.3
Chrysin*	Flavones	-8.8
Gardenin B		-6.4
Cirsilineol		-7.6
Hesperetin 3'-O-glucuronide	Flavanones	-8.4
Naringenin		-8.5
3-Methoxysinensetin	Flavonols	-6.2
5,6,7,3',4'-Pentahydroxyisoflavone	Isoflavonoids	-7.6
Carnosic acid	Phenolic terpenes	-7.5
Salvianolic acid B	Other polyphenols	-7.9

Gly220, and Arg221. However, unfavourable bonds between urolithin A and Gln266, and between chrysin and Phe182 and Tyr46 were present, depicted in red in Figure 2. These unfavourable bonds might have affected the ligand-protein binding due to repulsive interaction (Dhorajiwala et al. 2019). Unfavourable bonds were also present in the other ligand-protein complexes, except in cirsilineol, 5,6,7,3',4'-pentahydroxyisoflavone, and salvianolic acid, although having higher binding energy. The fact that ligands with low binding energy had unfavourable bonds indicated the possibility that repulsion effect was nullified by other types of interaction, as the attractive forces from favourable bonds were much stronger, hence low binding energy (Kukic & Nielsen 2010). However, unfavourable bonds might still impact the complex stability, thus should be interpreted along with molecular dynamics results.

All the eight lead ligands with promising binding energy bound with PTP1B at the same site and can be seen by the sharing of some residue interactions. The interactions mainly involved the catalytic binding site A and D (Liu et al. 2022). A site is the main catalytic site in PTP1B and the most accessible pocket, that contains a catalytic Cys215 and other residues, including Tyr46, Asp48, Val49, Phe182, Ala217, Ile219, and Gln262 (Liu et al. 2022). Because of its primary catalytic role, inhibition targeting this site is of high interest. However, targeting solely site A lacks of specificity since this site is highly conserved among other PTPs. On the other hand, D site is a narrow small pocket located near A site. D site does not have any biological implication in the insulin signalling pathway, yet targeting this site along with other sites may improve the specificity (Liu et al. 2022). It mainly involves Try46, Glu115, Lys120, Asp181, Phe182, Ser216, and Arg221 (Liu et al. 2022). With regards to these catalytic binding sites, it was shown in a study that PTP1B targeting site A and D, along with site C was the most promising among other catalytic inhibitors (Zhang & Du 2018).

Additionally, two hydroxide groups as good hydrogen donors and with aromatic rings that help stabilising their conjugated base that makes them even more superior donors. One hydroxide group bound with Arg221 via hydrogen bond, however, it clashed with Gln266 which also acted as a hydrogen donor. The hydroxide group and Phe182 in the chrysin showed hydrogen clash, and the ketone group and Tyr46, which are hydrogen acceptors, showed repulsion. The other interactions were brought about by the interaction of the π-π and π-σ orbitals between the ligands and amino acid residues, as well as by the presence of the phenolic aromatic rings.

Inhibition of PTP1B would help manage T2DM since it prevents the down-regulation of insulin signalling cascade which causes insulin resistance (Tautz et al. 2013; Liu et al. 2022). This investigation suggests that some phenolic compounds found in banana peel can bind to PTP1B and may potentially have an inhibitory effect. Their inhibitory effect towards PTP1B has not been extensively researched. However, the ability of several phenolic compounds to bind with PTP1B has been predicted by some *in silico* studies (Damián-Medina et al. 2020; Mechchate et al. 2021; Rath et al. 2022). This current work also found that the majority of the promising ligands were in the class of polyphenols, including flavones, flavanones, and isoflavonoids. With regards to that, Rath et al. (2022) also concluded the potential of several polyphenols as PTP1B inhibitors. Similarly, an *in vivo* investigation also revealed that an extract from *Cudrania tricuspidate* leaves high in polyphenols had a potent inhibitory effect on PTP1B (Kim et al. 2016).

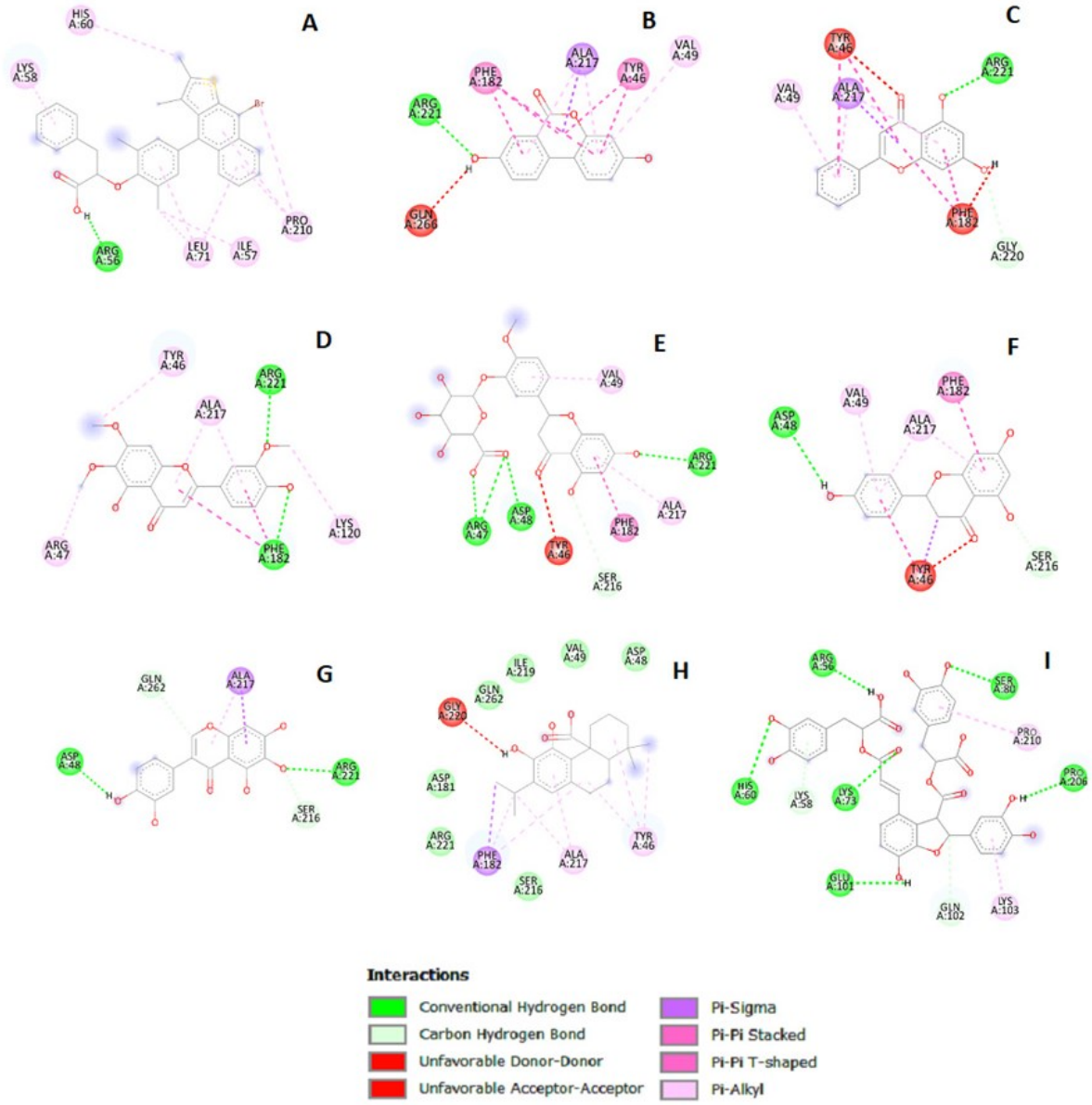

Figure 2. Visualisation of the interactions between ligands and amino acid residues of PTP1B. Interaction with ertiprotafib (A), urolithin A (B), chrysin (C), Cirsilineol (D), hesperetin 3'-O-glucuronide (E), naringenin (F), 5,6,7,3',4'-pentahydroxyisoflavone (G), carnosic acid (H), and salvianolic acid (I).

Absorption, Digestion, Metabolism, Excretion, and Toxicity (ADME-Tox) Analysis

Using ADMETlab 2.0 online program, drug-likeness according to Lipinski's Ro5 and other ADME-Tox criteria was predicted, as shown in Table 4. Drug-likeness is useful criterion for a new drug discovery because safe and approved medications have a window range of physicochemical properties that will display typical molecular behavior *in vivo* (Bickerton et al. 2012). Typically, Lipinski's Rule of Five is used to assess drug-likeness for oral bioavailability. If a compound violates no more than one rule, it is considered as a strong candidate. All of the potential leads passed Lipinski's Rule of Five, with the exception of hesperitin 3'-*O*-glucoronide. This indicates that hesperetin 3'-*O*-glucoronide may have low absorbability or permeability, making it an unsuitable option for an oral medication.

Almost all ligands had a good HIA and absent from BBB. A good HIA is needed since an orally administered drugs need to be absorbed through the intestinal lumen. The inability of the ligands to cross BBB

Table 4. ADME-Tox Prediction of the Ligands.

Compounds	Lipinski's Rule Viola-	HIA[b]	BBB Penetration[c]	Ames Toxicity[d]	Carcinogenicity[e]	Skin Sensiti-	Eye Irritation[g]	$LC_{50}FM$[h]	$LC_{50}DM$[i]
Ertiprotafib	2	---	---	---	-	+++	--	6.490	6.261
Urolithin A	0	---	---	---	+	+++	+++	4.890	5.129
Chrysin	0	---	---	+	-	+++	+++	5.066	5.220
Cirsilineol	0	---	---	-	---	+	++	5.120	6.587
Hesperetin 3'-O-glucuronide	2	+	---	--	--	--	---	4.790	5.404
Naringenin	0	---	---	--	+	+++	+++	6.692	6.410
5,6,7,3',4'-Pentahydroxyisoflavone	0	--	---	+	--	+++	+++	5.033	6.006
Carnosic acid	0	---	-	---	---	+++	++	4.573	5.604
Salvianolic acid B	1	---	---	---	-	--	-	7.044	7.223

Note: The prediction probability values are depicted into 6 symbols: 0 – 0.1 (---), 0.1 – 0.3 (--), 0.3 – 0.5 (-), 0.5 – 0.7 (+), 0.7 – 0.9 (++), and 0.9 – 1 (+++). HIA: Human Intestinal Absorption, BBB: Blood-Brain Barrier. [a]: accepted if no more than 1 violation exist; [b]: HIA+ = <30%, HIA- ≥30% absorption, value is probability being HIA+; [c] : probability of BBB+; [d] : probability of being toxic; [e] : probability of being toxic; [f] : probability of being sensitizer; [g] : probability of being irritants; [h] : 96-h lethal concentration to kill 50% of fathead minnow in -log[(mg/L)/(1000 x MW)]; [I] : 46-h lethal concentration to kill 50% *Daphnia magna* in -log[(mg/L)/(1000 x MW)].

showed low indication of toxicity to the brain. Interestingly, Ames test showed a positive result for chrysin and 5,6,7,3',4'-pentahydroxyisoflavone, but not in naringenin and urolithin A, and *vice versa* in carcinogenicity test. In this regard, Ames test mutagenicity and carcinogenicity should have a high correlation. However, mutagen in Ames test does not certain the carcinogenicity in human (Föllmann et al. 2013). Furthermore, almost all of them were irritants to the eyes and skin. Lastly, the environmental toxicity towards fathead minnow and *Daphnia magna* were comparable to the control.

Molecular Dynamics Simulation Analysis

Figure 3 shows the RMSF (root mean squared fluctuation) in the fluctuation plot of the complex between PTP1B and standard, urolithin A, and chrysin. As seen in the figure, the fluctuation of the amino acids still fell in the range of 1-3 Å, which is considered stable (Parikesit & Nurdiansyah 2021). However, some residues of PTP1B complex with both urolithin A and chrysin fluctuate significantly. The PTP1B-urolithin A complex had significant fluctuation in Arg43, Glu62, Asp63, Asn90, and Glu207, while in PTP1B-chrysin complex in Asp298. Differences in RMSF fluctuation between complexed with urolithin A and chrysin indicated that the ligand conformations affected the complex stability (Parikesit & Nurdiansyah 2021).

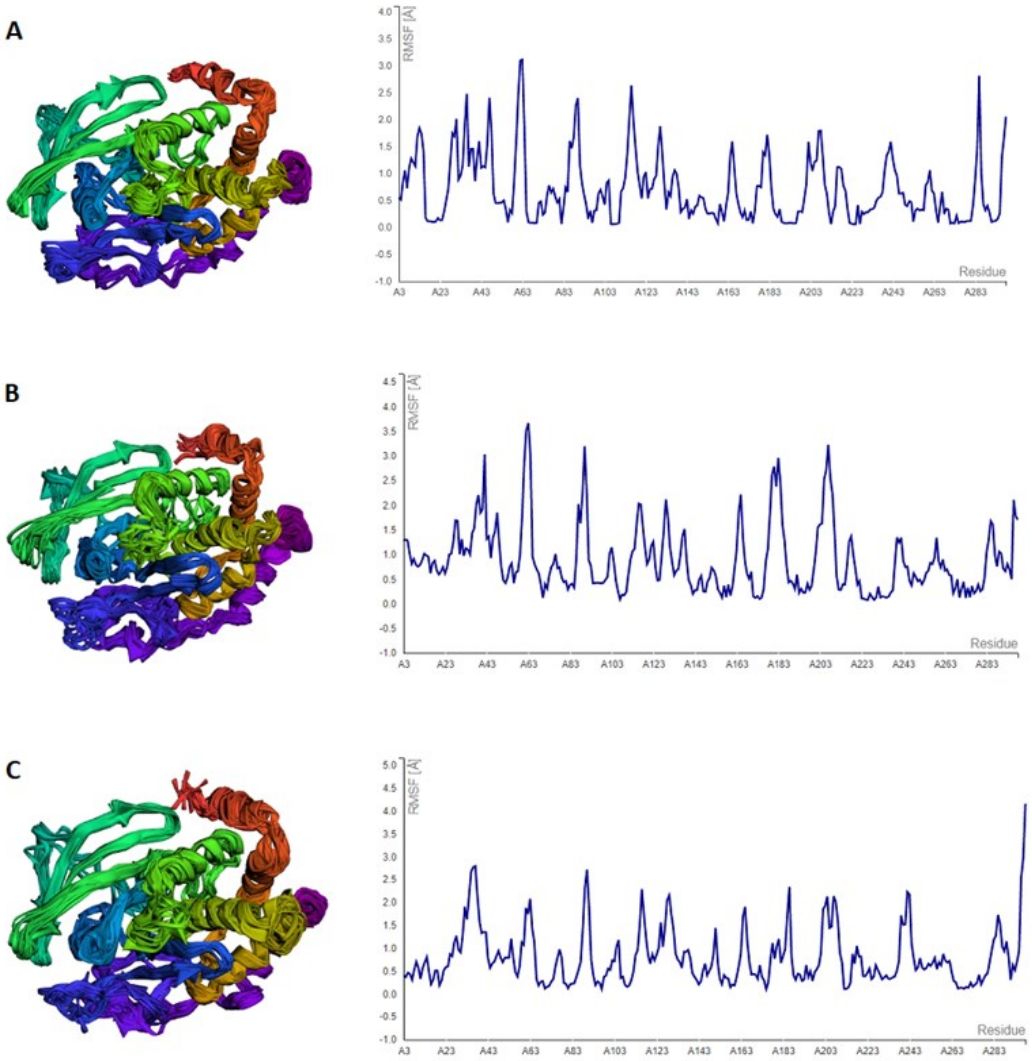

Figure 3. RMSF Fluctuation Plot. Ensemble of protein models are depicted on the left and fluctuation plot on the right for PTP1B complexes with (A) ertiprotafib (standard), (B) urolithin A, and (C) chrysin.

CONCLUSION

Forty-three phenolic compounds from banana peel have successfully been screened for their potential to inhibit PTP1B, a novel anti-diabetic target for the treatment of T2DM. Using PASS online, the potential ligands were converged down into 18 ligands that specifically inhibit PTP1B. Eight ligands with favorable binding energy were identified using molecular docking, with urolithin A and chrysin as the most favourable. Although they both met Lipinski's Rule of Five, had good HIAs, and lacked BBB penetration, their potential for mutagenicity, carcinogenicity, and skin and ocular sensitivity remained in questions. Both Urolithin A and Chrysin displayed a stable conformation with PTP1B in a molecular dynamic simulation. Hence, the current research suggests that urolithin A and chrysin are potential PTP1B inhibitors. Lastly, experimental *in vitro* and *in vivo* studies are required to validate the findings of this investigation.

AUTHORS CONTRIBUTION

R.A.P. conducted this research and wrote the original manuscript. A.A.P. conceptualised research idea, validated, and supervised this research. J.A. reviewed the manuscript and supervised this research.

ACKNOWLEDGMENTS

The authors would like to thank the Department of Research and Community Service of Indonesia International Institute for Life Sciences (RCS i3L) for their heartfelt support.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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