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# In-Silico Analysis of Polyphenol Compounds in Pomegranate Fruit *(Punica granatum L.)* Peel Potential as type 2 Antidiabetes Mellitus

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***Abstract***

*Diabetes mellitus is a disease characterized by increased blood sugar levels due to insulin resistance caused by the uncontrolled expression of the protein tyrosine phosphatase 1B (PTP1B). Several compounds that inhibit PTP1B have been studied, including polyphenol. Many studies have been conducted on diabetes medicines based on natural ingredients, including the pomegranate fruits (Punica granatum L). This study aims to test the inhibitory activity of polyphenolic compounds in pomegranate peel (gallic acid, caffeic acid, ellagic acid, chlorogenic acid, apigenin, quercetin, pelargonidin, and cyanidin) against PTP1B through molecular docking. The 3D structures of polyphenolic compounds were obtained from the PubChem database, while PTP1B was from the Protein Data Base. Molecular docking simulations were carried out using AutoDock Vina and several supporting softwares, such as Biovia Discovery Studio Client 4.1, AutoDockTools 1.5.6, PyMOL, and LigPlot. Molecular docking results showed that polyphenolic compounds from pomegranate peel have good inhibitory potential against PTP1B. It is proven by the binding affinity value for PTP1B, which is low and negative, namely in the range -6.4 to -8.4 kcal/mol, and the inhibition constant in the range 0.69 to 20,12 μM. The presence of phenol and carboxylic acid groups in polyphenol compounds can strengthen ligand-protein complexes through hydrogen bonds, especially with the amino acid residues Gln221 and Cys215. The potential of polyphenolic compounds as antidiabetics is also supported by van der Waals interactions and π-π stacking interactions with PTP1B. Based on the molecular docking test that has been carried out, it can be concluded that the polyphenolic compounds in pomegranate peel have the potential to act as type 2 anti-diabetes mellitus.*

***Keywords:*** *diabetes mellitus; pomegranate peel; PTP1B; polyphenols, in-silico*

## Introduction

Diabetes mellitus is a disease caused by metabolic disorders in the body and is characterized by symptoms of increased blood sugar levels (Kumar et al., 2020). The number of type 2 diabetes mellitus patients is increasing every year, especially in Indonesia. The International Diabetes Federation (IDF) reported around 463 million diabetes sufferers worldwide in 2019, which will increase to 578 million in 2030. In 2045, it is estimated to reach 700 million (Cho et al., 2018). IDF also projects that people living with diabetes in Indonesia are ranked 7$^{th}$ in the world with 10.7 million people. Indonesia is the only country with the most significant number of people with diabetes in Southeast Asia (Infodatin, 2020). Apart from being the cause of premature death throughout the

world, diabetes is also the leading cause of chronic kidney disease, heart disease, and blindness (Padhi et al., 2020).

Type 2 diabetes mellitus is formed as a result of insulin resistance caused by genetic factors and an unhealthy lifestyle (Bagri et al., 2009). One of the causes of insulin resistance is the uncontrolled expression of the protein tyrosine phosphatase 1B (PTP1B). PTP1B can prevent the binding of insulin to the insulin receptor through dephosphorylation of the insulin receptor, thereby disrupting the process of glucose metabolism in the blood and resulting in type 2 diabetes mellitus (Zou et al., 2016). Several literature reviews show that inhibition of the function of protein tyrosine phosphatase 1B (PTP1B) is an appropriate alternative treatment for type 2 diabetes mellitus (Pujiastuti et al., 2017).

Many studies have been carried out on diabetes medicines based on natural ingredients, including the pomegranate fruit *(Punica granatum L.)*. Ethanol extract from pomegranate leaves has been studied to reduce sugar levels in mice induced by alloxan (Gharib et al., 2019). The antidiabetic activity of pomegranate flower and leaf extracts was also tested in vitro by inhibiting the α-glucosidase enzyme, with an $IC_{50}$ value of 45.31 µg/ml (Yuan et al., 2012). Ethanol extract from pomegranate peel was studied to reduce blood sugar levels with a significant value ($p<0.05$) (Das et al., 1970). Apart from having the potential to reduce blood sugar levels, the pomegranate fruit is also reported to have various other activities such as an antioxidant, anti-cholesterol, anti-cancer, and anti-osteoporosis (Fourati et al., 2020).

The various pharmacological activities of the pomegranate fruit cannot be separated from the activity of its contained compounds. Pomegranate contains various minerals, acids, polysaccharides, polyphenols, vitamins, and anthocyanins (Maphetu et al., 2022). Pomegranate seeds and leaves have been studied to contain flavonoids, alkaloids, and several acid compounds, such as linoleic acid, coumaric acid, and gallic acid (Ranjha et al., 2023). Pomegranate peel is rich in flavonoids, polyphenolic compounds, and tannins, which have the potential to be anticarcinogenic, antibacterial, and antioxidant. Polyphenolic compounds in pomegranate peel include naringenin, gallic acid, ferulic acid, kaempferol, quercetin, punicalagin, and epicatechin (Nge et al., 2020). These polyphenolic compounds have the potential for pharmacological activity because they contain phenol groups (Tanase et al., 2019). In silico, the compounds gallic acid, punicalin, and punicalagin in pomegranate peel have high potential as antidiabetics, as seen from their inhibitory power against several proteins that play a role in diabetes regulation (Gull et al., 2023).

Several studies on PTP1B inhibition as an alternative treatment for diabetes have been carried out in silico and in vitro. *Hizikia fusiformis* extract, which contains phenolic and terpenoid compounds, has an $IC_{50}$ value of 6–23 µM, and the valoneic acid dilactone compound in pomegranate peel has an inhibitory power against PTP1B of 12.4 µg/ml (Srividya et al., 2023). Apart from that, several in silico studies show that compounds with phenol groups have the potential to inhibit the action of PTP1B (Barik et al., 2020; Rath et al., 2022). The phenol group in mangiferin can hydrogen bond with the amino acids GLN-78 and ARG-79 on the active site of PTP1B (Pujiastuti et al., 2017). The phenol group in the *α-mangostin* compound is also essential in PTP1B inhibition through hydrogen bonds with 3 amino acids on the active (Hartanti et al., 2022). Therefore, this study aims to test the inhibition of polyphenolic compounds found in pomegranate peel against PTP1B.

## Methods

### Tools and Materials

The device used in this research is an Asus Vivobook laptop with AMD Ryzen 5 3500U processor specifications, 8.00 GB of RAM, and the Windows 10 operating system. AutoDockTools 1.5.6, AutoDock Vina, PyMOL Biovia Discovery Studio Client 4.1, and LigPlot are some software used in this research. The 3D structure of the PTP1B protein was downloaded from the Protein Data Bank (PDB) (https://www.rcsb.org). The ligands used in this research were polyphenolic compounds from pomegranate peel like gallic

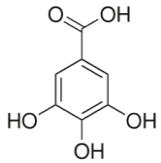
acid, caffeic acid, chlorogenic acid, ellagic acid, apigenin, quercetin, pelargonidin, and cyanidin (Singh et al., 2018). The 3D structure of the ligand was obtained from the Pubchem data bank (https://www.pubchem.com).

## Work Procedure

*Ligand and Protein Preparation*

The 3D structure of protein tyrosine phosphatase 1B (PTP1B) was downloaded from the Protein Data Bank (PDB) with ID code 4Y14. In contrast, the 3D structure of the polyphenol compound ligand (Figure 1) was downloaded from the Pubchem data bank (https://www.pubchem.com) with codes gallic acid (CID: 370), caffeic acid (CID: 689043), chlorogenic acid (CID: 1794427), ellagic acid (CID: 5281855), apigenin (CID: 5280443), quercetin (CID: 5280343), pelargonidin (CID: 440832), and cyanidin (CID: 128861).

PTP1B protein preparation was carried out using AutodockTools 1.5.6 software to clean protein molecules from water molecules and other molecules that are not needed. The protein structure that has been cleaned is then added with charges and polar hydrogen and saved in PDBQT format. Ligand structures obtained from the Pubchem data bank were first converted into PDB format using Biovia Discovery Studio Client 4.1 software and prepared using AutoDockTools 1.5.6 by assigning charges, analyzing bond rotations on the ligand, and re-saving the ligand in the form of PDBQT. Apart from that, at this preparation stage, grid box measurements were also carried out by adjusting the active side of the protein using AutoDockTools 1.5.6.

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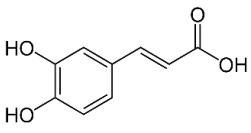


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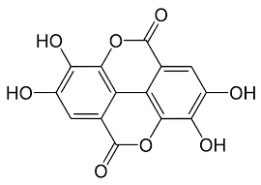


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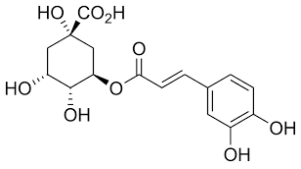


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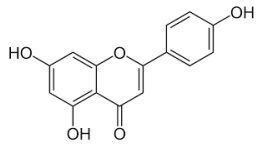


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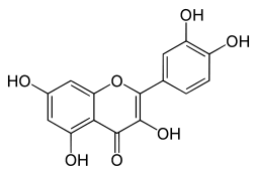


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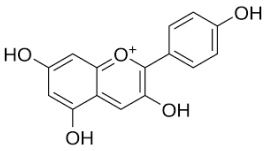


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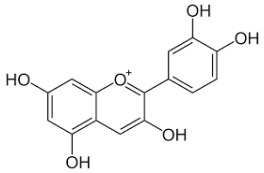


**(h)**

Figure 1. Structure of polyphenolic compounds in pomegranate peel (a) gallic acid (b) caffeic acid (c) ellagic acid (d) chlorogenic acid (e) apigenin (f) quercetin (g) pelargonidin (h) cyanidin

*Validation of Molecular Docking Methods*

The molecular docking method was validated by redocking the initial substrate (native ligand) with the PTP1B protein using Autodock Vina. The aim of validating this docking method is to test the accuracy of the grid box size used in the molecular docking process. The results of the redocking analysis are seen through the root mean square deviation (RMSD) value between the native ligand resulting from redocking and the native ligand from the PDB using PyMOL software. The molecular docking method that will be carried out is declared valid if the RMSD value is ≤ 2.0 Å. (Morris et al., 2008). The grid box size used in this research is 22x18x16 with coordinates x (-10,597), y (-22,120), and z (-8,056).

*Molecular Docking*

The antidiabetic activity of polyphenolic compounds was measured via molecular docking against PTP1B using AutoDock Vina software. The results of molecular docking

between the ligand and the protein were then analyzed using PyMOL to see the position of the polyphenolic compound in the active side pocket of the PTP1B protein. Next, the interactions between polyphenolic compounds and PTP1B were analyzed using LigPlot and the Biovia Discovery Studio Visualizer.

**Results and Discussion**

The potential of polyphenolic compounds as type 2 antidiabetes mellitus was measured by their inhibitory power against PTP1B (Protein Tyrosine Phosphatase 1B) through molecular docking simulations. PTP1B is a protein that plays a role in a series of insulin signal transductions, dephosphorylating the insulin receptor when it binds to insulin (Rath et al., 2022). High expression of PTP1B can prevent insulin binding to the insulin receptor, thereby inducing insulin resistance and causing type 2 diabetes mellitus (Zou et al., 2016). The PTP1B protein structure used in this study is human PTP1B obtained from the PDB with code 4Y14 (Figure 2). The protein structure used during the molecular docking process is the A-chain PTP1B protein structure, which binds to a native ligand in the form of the compound 3-bromo-4-[difluoro(phosphono)methyl]-N-methyl-Nalpha-(methylsulfonyl)-L-phenylalanine.

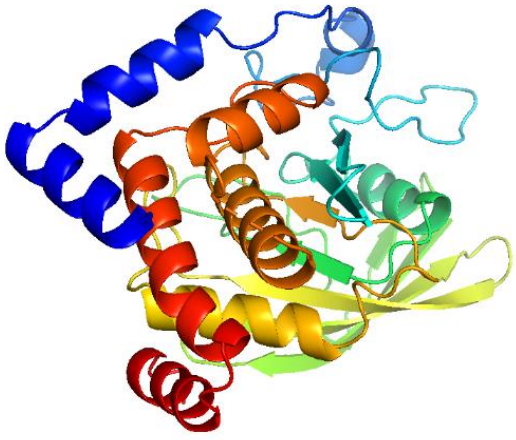

Figure 2. 3D structure of the PTP1B protein (ID: 4Y14)

The molecular docking validation process in this research was carried out by redocking the native ligand compound with the PTP1B protein using AutoDock Vina software. This test also aims to determine the suitability of the grid box size used during the molecular docking process and is said to be valid if the RMSD value is less than 2 Å (Mohanty et al., 2020). Based on the results of the validation that has been carried out, it can be seen that the structure of the native ligand resulting from redocking with the initial native ligand coincides with an RMSD value of 1.199 Å (Figure 3). This shows that the grid box size used in this research is appropriate and valid for use in the molecular docking process of polyphenolic compounds. This redocking process also produces a native ligand binding energy affinity of -8.8 kcal/mol with an inhibition coefficient of 0.35 µM.

Figure 3. Visualization of validation results of the molecular docking method (green: initial native ligand, purple: native ligand resulting from redocking)

The potential of polyphenolic compounds from pomegranate peel as antidiabetics can be measured by their ability to inhibit the activity of protein tyrosine kinase 1B (PTP1B) through molecular docking simulations. The inhibitory ability of polyphenolic compounds against PTP1B can be analyzed through the low binding energy and interactions between the ligand compound and the protein's active site (Damián et al., 2020). The bond energy produced during molecular docking will affect the conformational stability of the complex between the ligand and protein, where the lower the bond energy, the more stable the complex formed (Guedes et al., 2014). Table 1 shows that all polyphenolic compounds that have been tested have low binding energies and have negative values around -6.4 to -8.4 kcal/mol. It shows that the

polyphenolic compounds in pomegranate peel can quickly form bonds and interact well with the active site of the PTP1B protein. Of all the polyphenolic compounds that have been tested, the ellagic acid compound has the most negative binding affinity, -8.4 kcal/mol. The compounds caffeic acid, apigenin, pelargonidin, quercetin, and cyanidin have almost the same binding affinity, around -7.1 to -7.6 kcal/mol.

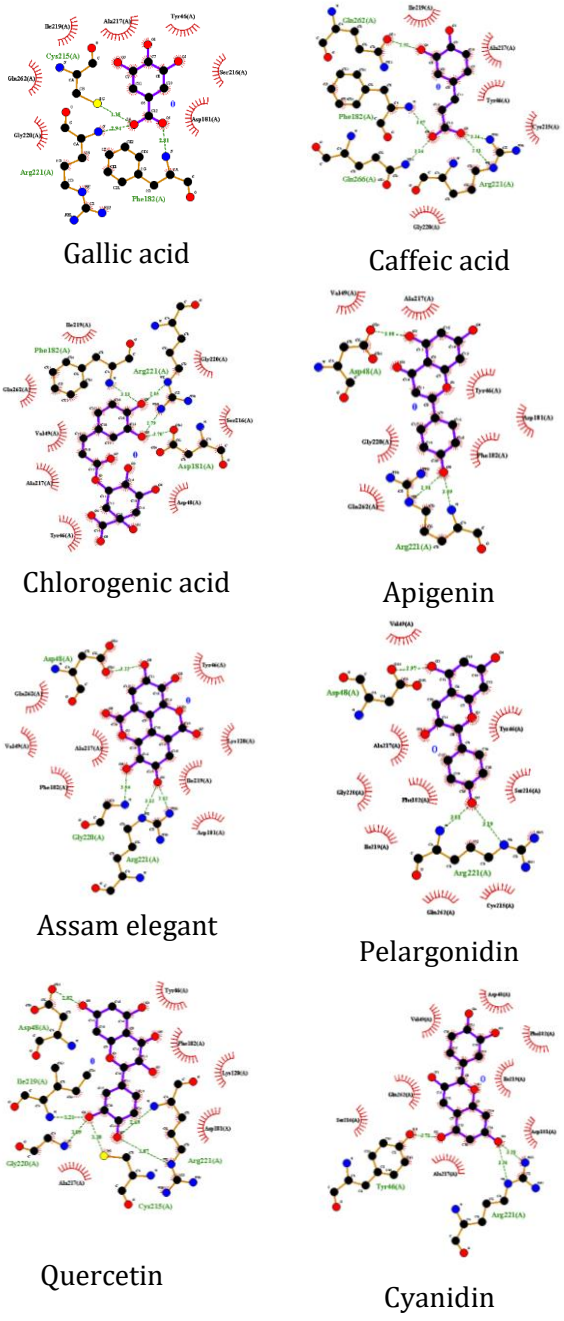


Figure 4. Interaction of polyphenolic compounds with the active site of PTP1B

Besides the binding affinity between polyphenolic compounds and the PTP1B protein, the complexity of the ligand-protein bond is also influenced by the value of the inhibition coefficient (Ki). The inhibition coefficient (Ki) value generally indicates the concentration required for a ligand to inhibit a protein ((Ha et al., 2018). Therefore, the smaller the value of the inhibition coefficient (Ki) and the lower the concentration of the ligand compound, the more capable it is to inhibit the action of a protein or macromolecule. Thus, the smaller the inhibition coefficient value, the better the potential of the ligand for inhibiting proteins (Hartanti et al., 2022). In Table 1, it can be seen that the ellagic acid compound with the most negative binding affinity value also has the lowest inhibition coefficient value, 0.69 µM, followed by the compounds apigenin and pelargonidin, 2.65 and 3.71 µM.

The potential of polyphenolic compounds to inhibit the PTP1B protein is also determined by the interaction between the polyphenolic compounds and the active site of the PTP1B protein. Hydrogen bonds, hydrophobic interactions, and π-π stacking can strengthen the complexes formed between ligands and proteins (Shaker et al., 2021). Based on the analysis using LigPlot in Figure 4, it can be seen that all polyphenolic compounds have good interactions with the active site of the PTP1B protein, both through hydrogen bonds and hydrophobic interactions. Overall, polyphenolic compounds can hydrogen bond with amino acid residues in the active site of PTP1B, especially the amino acid residues Arg221 and Cys215, which are vital amino acids in the catalytic system of the PTP1B protein (Wu et al., 2018). The polyphenol compounds with the most hydrogen bonds are quercetin and caffeic acid. The quercetin compound has six hydrogen bonds at the active site of PTP1B, namely with the amino acid residues Asp48, Arg221, Ile219, Gly220, and Cys215. In comparison, the caffeic acid compound has five hydrogen bonds with the amino acid residues Phe182, Gln262, and Arg221.

Table 1. Molecular docking results of polyphenolic compounds from pomegranate peel against the PTP1B protein

| Compound | Energy (kcal/mol) | Inhibition Coefficient (μM) | Hydrogen Bond | Hydrophobic Interaction |
|---|---|---|---|---|
| Gallic acid | -6.4 | 20.12 | Phe182 (2.81 Å)<br>Cys215 (3.25 Å)<br>Arg221 (2.94 Å) | Asp181. Tyr46. Ser216. Ala217. Ile219. Gly220. Gln262 |
| Caffeic acid | -7.1 | 6.16 | Phe182 (3.07Å)<br>Gln262 (2.93Å)<br>Gln266 (3.14Å)<br>Arg221 (3.34Å)<br>Arg221 (2.81Å) | Gly220. Cys215. Tyr46. Ala217. Ile219 |
| Ellagic Acid | -8.4 | 0.69 | Asp48 (3.22Å)<br>Arg221 (2.82Å)<br>Arg221 (3.12Å)<br>Gly220 (3.04Å) | Tyr46. Lys120. Asp181. Ile219. Ala217. Gln262. Val49. Phe182 |
| Chlorogenic acid | -6.9 | 8.64 | Asp181 (2.70Å)<br>Phe 182 (3.13Å)<br>Arg221 (2.79Å)<br>Arg221 (2.85Å) | Asp48. Ser216. Gly220. Ile219. Gln262. Val49. Ala217. Tyr46 |
| Apigenin | -7.6 | 2.65 | Asp48 (3.00Å)<br>Arg221 (2.91Å)<br>Arg221 (3.09Å) | Tyr46. Asp181. Phe182. Gly220. Gln262. Val49. Ala217 |
| Quercetin | -7.2 | 5.21 | Asp48 (2.82Å)<br>Arg221 (3.07Å)<br>Arg221 (2.69Å)<br>Ile219 (3.21Å)<br>Gly220 (3.09Å)<br>Cys215 (3.30Å) | Tyr46. Phe182. Lys120. Asp181. Ala217 |
| Pelargonidin | -7.4 | 3.71 | Asp48 (2.97Å)<br>Arg221 (3.01Å)<br>Arg221 (3.19Å) | Tyr46. Ser216. Cys215. Glu262. Ile219. Phe182. Gly220. Ala217. Val49 |
| Cyanidin | -7.1 | 6.16 | Tyr46 (2.71Å)<br>Arg221(3.28Å)<br>Arg221 (3.26Å) | Asp48. Phe182. Ile219. Asp181. Ala217.Ser216. Gln262. Val49 |

The hydrogen bonds between polyphenolic compounds and the active site of PTP1B depend on their position and functional group (Proença et al.. 2018). One of the functional groups of polyphenol compounds that plays an essential role in hydrogen bonds is the hydroxy group attached to the aromatic ring (phenol group).

The phenol group can act as an electron donor or acceptor in hydrogen bonds. It shows that the presence of the phenol group can strengthen its inhibitory activity against PTP1B. Besides the phenol group, hydrogen bonds formed between polyphenol compounds and the active site of PTP1B also occur through the carboxylic acid group. Gallic acid hydrogen bonds through the carboxylic acid functional group with the three amino acid residues Phe182, Cys215, and Arg221, while the carboxylic acid group in caffeic acid has four hydrogen bonds with the amino acid residues Phe182, Gln266, and Arg221. Polyphenolic compounds such as chlorogenic acid, ellagic acid, apigenin, quercetin, pelargonidin, and cyanidin only hydrogen bond with PTP1B via the phenol group attached to the aromatic ring. Based on the results of the analysis that has been carried out, it can be said that hydrogen bonding interactions in polyphenol compounds with PTP1B mainly occur through the phenol group, and some compounds can bond hydrogen through the carboxylic acid group.

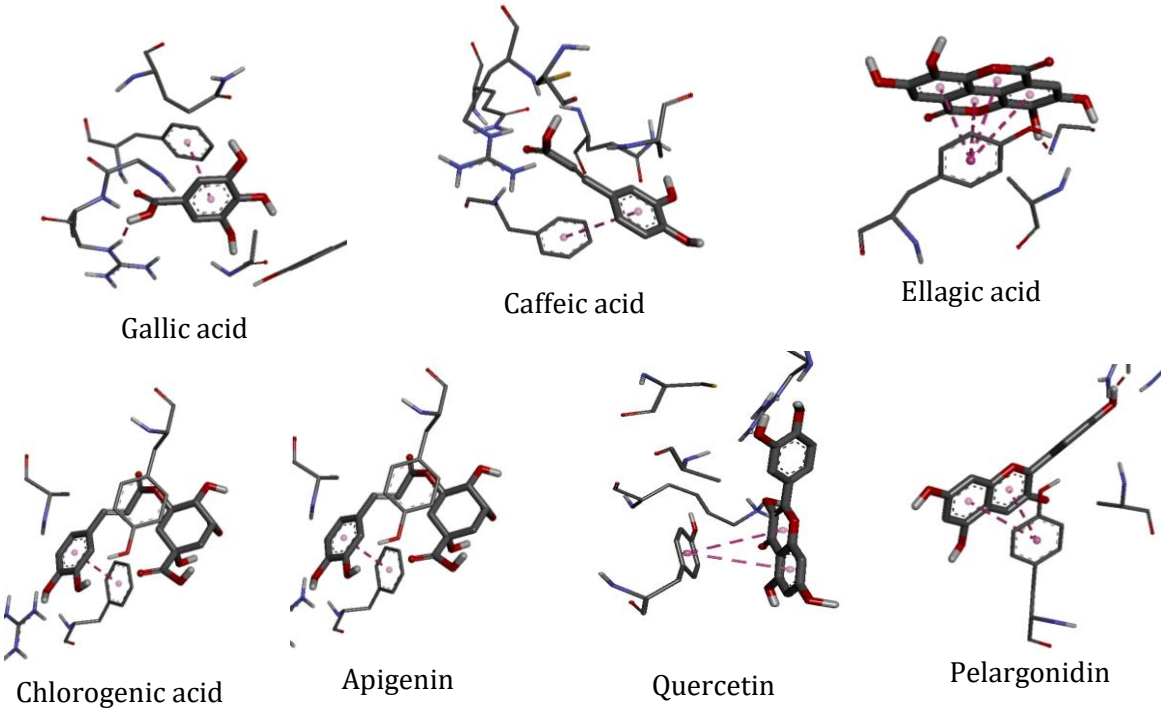


Figure 5. Interaction of π-π stacking of polyphenolic compounds with the active site of PTP1B

Besides hydrogen bonds, the number of hydrophobic interactions, such as van der Waals interactions and π-π stacking, also affects the stability of the ligand and protein complexes (Chen et al. 2018). All polyphenolic compounds can interact in a van der Waals manner with five to nine amino acid residues in the active site of PTP1B. The pelargonidin compound has the most van der Waals interactions with the amino acid residues Tyr46, Ser216, Cys215, Glu262, Ile219, Phe182, Gly220, Ala217, and Val49. The inhibitory ability of this polyphenol compound is also supported by the π-π stacking interaction between the polyphenol aromatic ring and the amino acids Phe182 and Tyr46 (Figure 5). All polyphenolic compounds, except cyanidin compounds, can interact by π-π stacking with PTP1B. The compounds gallic acid, caffeic acid, and chlorogenic acid can interact π-π stacking with the amino acid residue Phe182.

In contrast, ellagic acid, quercetin, and pelargonidin interact π-π stacking with the amino acid residue Tyr46. The apigenin compound can interact by π-π stacking with both amino acid residues Phe182 and Tyr46. Therefore, aromatic rings in polyphenolic compounds can also increase their inhibitory power against PTP1B. Based on the overall results of the molecular docking tests that have been carried out, it can be seen that the polyphenolic compounds in pomegranate peel have the potential to inhibit the PTP1B protein.

## Conclusions

Based on the results of the research, it can be concluded that polyphenolic compounds from pomegranate *(P. granatum L.)* peel have the potential to act as type 2 antidiabetes mellitus. This is proven by the binding affinity value for PTP1B, which is low and has a negative value, in the range of -6.4 up to -8.4 kcal/mol, and an inhibition constant in the range of 0.69 to 20.12 μM. The potential of polyphenolic compounds as antidiabetics is also supported by their ability to interact with amino acid residues on the active site of the PTP1B protein through hydrogen bonds, especially with amino acid residues Gln221 and Cys215, van der Waals interactions, and π-π stacking interactions. In vitro and in vivo testing of these polyphenolic compounds is necessary to further validate in silico test results.

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