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Melani Sinastri Renagupita
Medical Education Study Program, Faculty of Medicine, Universitas Hang Tuah Surabaya, Surabaya 60111, Indonesia, melanis.renagupita@gmail.com

Rahadianto Rahadianto
Department of Clinical Pathology, Universitas Hang Tuah Surabaya, Surabaya 60111, Indonesia

Efyluk Garianto
Department of Public Health Sciences, Universitas Hang Tuah Surabaya, Surabaya 60111, Indonesia

Herin Setianingsih
Department of Anatomy, Universitas Hang Tuah Surabaya, Surabaya 60111, Indonesia

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Potential Effect of Phlorotannins in Brown Algae for Antidiabetic Therapy: Molecular Docking Approach

Melani Sinastri Renagupita[1*], Rahadianto[2], Efyluk Garianto[3], and Herin Setianingsih[4]

1. Medical Education Study Program, Faculty of Medicine, Universitas Hang Tuah Surabaya, Surabaya 60111, Indonesia
2. Department of Clinical Pathology, Universitas Hang Tuah Surabaya, Surabaya 60111, Indonesia
3. Department of Public Health Sciences, Universitas Hang Tuah Surabaya, Surabaya 60111, Indonesia
4. Department of Anatomy, Universitas Hang Tuah Surabaya, Surabaya 60111, Indonesia

E-mail: melanirena.fk18@hangtuah.ac.id

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Abstract

This study aims to manifest the effect of the active compound phlorotannins in brown algae on decreasing insulin resistance by analyzing the predicted interaction between phlorotannins and protein tyrosine phosphatase 1B (PTP 1B) and estimating the pharmacokinetics and toxicity of the active compound for type 2 diabetes mellitus (DM) therapy. This type of research uses an in silico study to test the effect of using phlorotannins as an active compound in brown algae against PTP 1B inhibition. Starting from preparing materials, i.e., downloading the three-dimensional structure of phlorotannins via PubChem and PTP 1B via RSCB PDB (PDB 1A5Y), molecular docking using Molegro Virtual Docker 5, molecular visualization using PyMol and Discovery Studio, and predicting pharmacokinetics and toxicity via pkCSM have been conducted. Here, the phlorotannins include phloroglucinol, dioxinodehydroeckol, eckol, phlorofucofuroeckol-A, dieckol, 7-phloroeckol, and 6,6′-bieckol. In addition, Ertiprotafib and S-phosphocysteine are used here as the comparison controls for docking validation. All phlorotannins can bind to PTP 1B at the same binding site with drug control. Experimental results revealed that phlorotannins–PTP 1B produces lower energy than complex S-phosphocysteine–PTP 1B (−266.8 kJ/mol), which acts as a control here. However, phloroglucinol–PTP 1B produces (−208 kJ/mol) under the same condition. Compared with the drug control Ertiprotafib (−322.8 kJ/mol), the lower bond energy is owned by phlorofucofuroeckol-A (−370.6 kJ/mol), 7-phloroeckol (−328 kJ/mol), dieckol (−331.8 kJ/mol), and 6.6'-bieckol (−341 kJ/mol). Furthermore, phlorotannins are very well absorbed in the intestine. According to Lipinski's rule, active compounds, such as phloroglucinol, eckol, and dioxinodehydroeckol have high potential as a drug. Phlorotannins are nontoxic against hepatocytes and have fewer side effects than drug control. Based on the obtained data, use of the active compound phlorotannins in brown algae can decrease insulin resistance, which can be employed as adjunctive therapy in type 2 DM.

Keywords: brown algae, in silico, insulin resistance, phlorotannins, PTP 1B

Introduction

Diabetes mellitus (DM) is a disease associated with metabolism abnormalities resulting from the absolute or relative deficiency of the insulin hormone, characterized by chronic hyperglycemia and high morbidity and mortality rates due to different complications [1, 2]. Although still controversial, almost all studies support that abnormalities in insulin secretion are initiated with insulin resistance, further promoting type 2 DM [3].

The goal of the therapy for patients with DM is to eliminate symptoms or slow down or even prevent further complications. However, pharmacological treatments with synthetic drugs have several problems, such as high prices, not an entirely effective treatment, and unwanted side effects from long-term use. Therefore, a breakthrough is required to discover and develop natural-based antidiabetic drugs with affordable prices and minimal side effects, especially in managing type 2 DM [4].

Most brown algae contain polyphenols formed by polymerizing phloroglucinol and derivate secondary metabolites known as phlorotannins [5]. Phlorotannins contained in brown algae are derivatives of polyphenols that have an inhibitory effect, one of which is against the enzyme protein tyrosine phosphatase 1B (PTP 1B) and acts as an antidiabetic [6]. PTP 1B is an intracellular enzyme that interferes with insulin signaling pathways.

The high level of PTP 1B hinders insulin from binding toward insulin receptors (IRs), thereby increasing insulin resistance. In other words, the inhibition of the PTP 1B enzyme can be a therapeutic modality for type 2 DM treatment, especially to improve insulin sensitivity [5].

Methods

This research uses a type of exploratory computational research (in silico) to examine the effect of using the active compound phlorotannins in brown algae against PTP 1B inhibition. The algae species containing these phlorotannins are *Ecklonia sp.*, such as *E. bicyclis*, *E. stolonifera*, and *E. cava* [5].

Protein and ligand structure preparation. Active compound phlorotannins in brown algae are available in PubChem (https://pubchem.ncbi.nlm.nih.gov/), which includes phloroglucinol (CID 359), phlorofucofuroeckol-A (CID 130976), eckol (CID 145937), dioxinodehydroeckol (CID 10429214), 7-phloroeckol (CID 10480940), dieckol (CID 3008868), and 6,6′-bieckol (CID 137388). The structure of PTP 1B was downloaded from the Protein Data Bank (RSCB PDB) (https://www.rcsb.org/) with PDB ID 1A5Y. The PTP 1B active site's prediction use predicted binding cavities with a maximum van der Waals parameter of 5.

Molecular docking. PTP 1B interacted with compound active phlorotannins and comparator control with Molegro Virtual Docker version 5.0. This study used a flexible docking via grid modification. The ligands were redocked to PTP 1B protein at the active sites, i.e., X = 45Å, Y = 15 Å, and Z = 3.06 Å. Ertiprotafib (CID 157049) and S-phosphocysteine (PDB ID 1A5Y) were used as controls. For validating the docking method of phlorotannins in brown algae, we used the native ligand (S-phosphocysteine), and Ertiprotafib was used for ligand comparison. The docking results were visualized to obtain 3D and 2D structures of the compound and protein complex PTP 1B. Parameter docking used grid-based MolDock score (GRID) function with a resolution of 0.30 A°, root mean square deviation less than 2, model number of 5, and docking of 10. The affinity value was obtained from the average MolDock summation, MolDock grid score, and rerank scores. The 3D and 2D structure visualization and analysis of the docking results used the PyMol and Discovery Studio version 21.1.1 software.

Absorption, distribution, metabolism, and excretion (ADME) prediction. ADME prediction was made by predicting small-molecule pharmacokinetic properties using graph-based signatures (pkCSM) [7]. Next, the analysis was performed to determine the physicochemical and pharmacokinetic active compounds that can become drugs. The results were reviewed through Lipinski's rule-of-five parameters [8]: a) *Hydrogen bond donors* (total nitrogen–hydrogen bonds, oxygen-hydrogen) less than or equal to 5; b) *Hydrogen bond acceptors* (all nitrogen or oxygen atoms) less than or equal to 10; c) Molecular weight < 500 g/mol; d) Log *P* value < 5 (Mlog$P$ < 4.15)

Toxicity prediction. Toxicity prediction was performed by predicting small-molecule pharmacokinetic properties using graph-based signatures (pkCSM) [7]: 1) Lethal dose 50 (LD50) is the administration dose of a compound or substance, which resulted in the death of 50% of all the tested subjects, and it is expressed in units of mg/kg body weight (mg/kg); 2) The toxicity classes according to the *Globally Harmonized System* are as follows [9]: a) Class I: fatal if swallowed (LD50 5); b) Class II: fatal if swallowed (5 < LD50 50); c) Class III: toxic if swallowed (50 < LD50 300); d) Class IV: harmful if swallowed (300 < LD50 2000); e) Class V: possibly harmful if swallowed (2000 < LD50 5000); f) Class VI: nontoxic (LD50 > 5000)

Results and Discussion

Interaction analysis active compound phlorotannins with PTP 1B. The 3D view of the active compound complex shows that the active compound phlorotannins bind to PTP 1B at the same binding region as the control (Figure 1). It is supported by the active site residues of each interaction between the active compound phlorotannins and PTP 1B (Figure 2). The bonds between the active compounds and the target proteins include van der Waals, hydrogen bonding, hydrophobic interactions, electrostatic, and unfavorable bonds (Figure 2). Based on the active compound–complex phlorotannins with PTP 1B, the active compound of brown algae has an antidiabetic activity via inhibiting PTP 1B, whose function is to phosphorylate. Tyrosine protein phosphorylation is one of the important mechanisms in controlling the growth, differentiation, and regulation of cell function [10]. PTP 1B catalyzes the dephosphorylation of the tyrosine residue (pY1162/pY1163) of the activated IR β-subunit and IR substrate-1 (IRS-1) [11]. The dephosphorylation of the IR by PTP 1B can stop the action of insulin, thus triggering insulin resistance. Therefore, the phosphorylation sequence plays a role in increasing or decreasing insulin sensitivity through the IRS activity in regulating carbohydrate, fat, and protein metabolism processes. For example, glucose transporters move toward cell membranes to help transport glucose in the blood to the cells [12].

From the image data, interactions between proteins and the ligands of each active compound phlorotannins and controls have active sites in areas, such as the interaction between protein and control (Ertiprotafib and S-phosphocysteine) (Figure 1). The same active site residue between the active compounds phlorotannins and Ertiprotafib indicated that phlorotannins are antidiabetic with the same inhibitory mechanism as Ertiprotafib. In

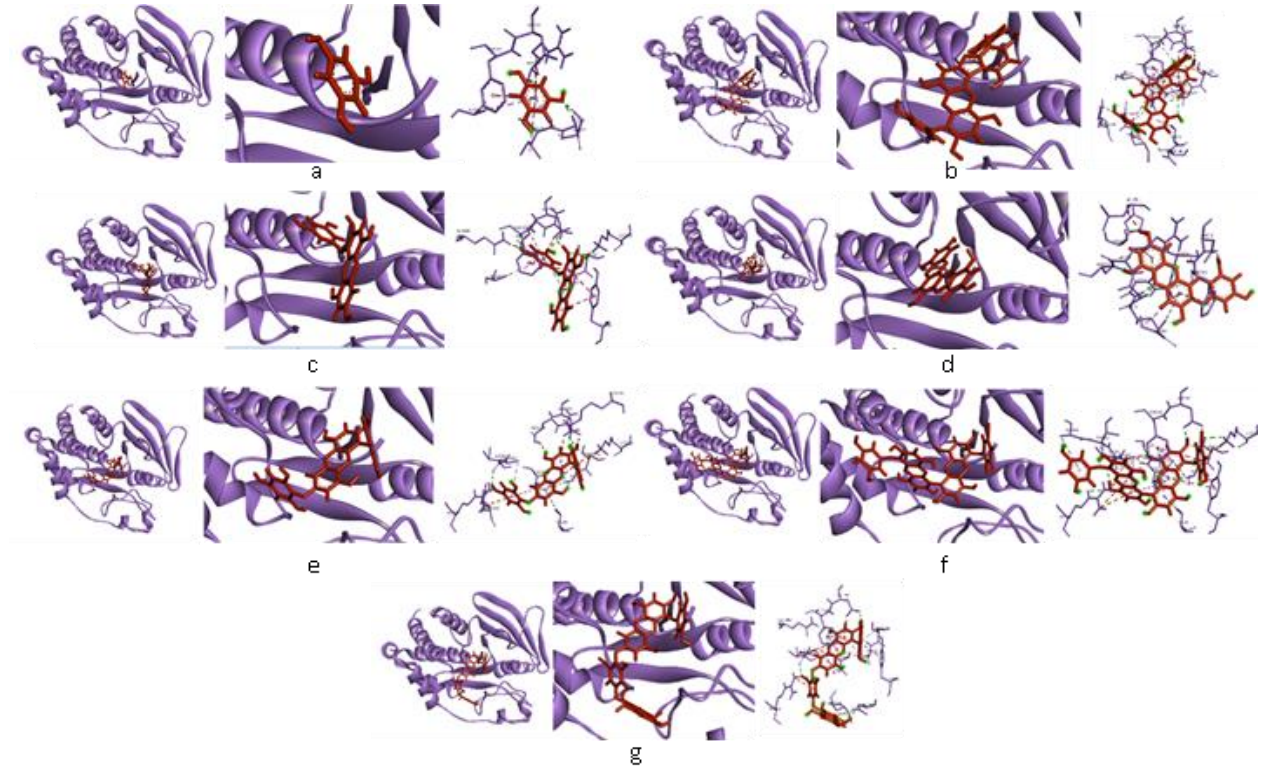


Figure 1. 3D Structure of the Phlorotannin Complex Against PTP 1B: a. Phloroglucinol–PTP 1B, b. Phlorofucofuroeckol-A–PTP 1B, c. Eckol–PTP 1B, d. Dioxinodehydroeckol–PTP 1B, e. 7-Phloroeckol–PTP 1B, f. Dieckol–PTP 1B, g. 6,6′-Bieckol–PTP 1B

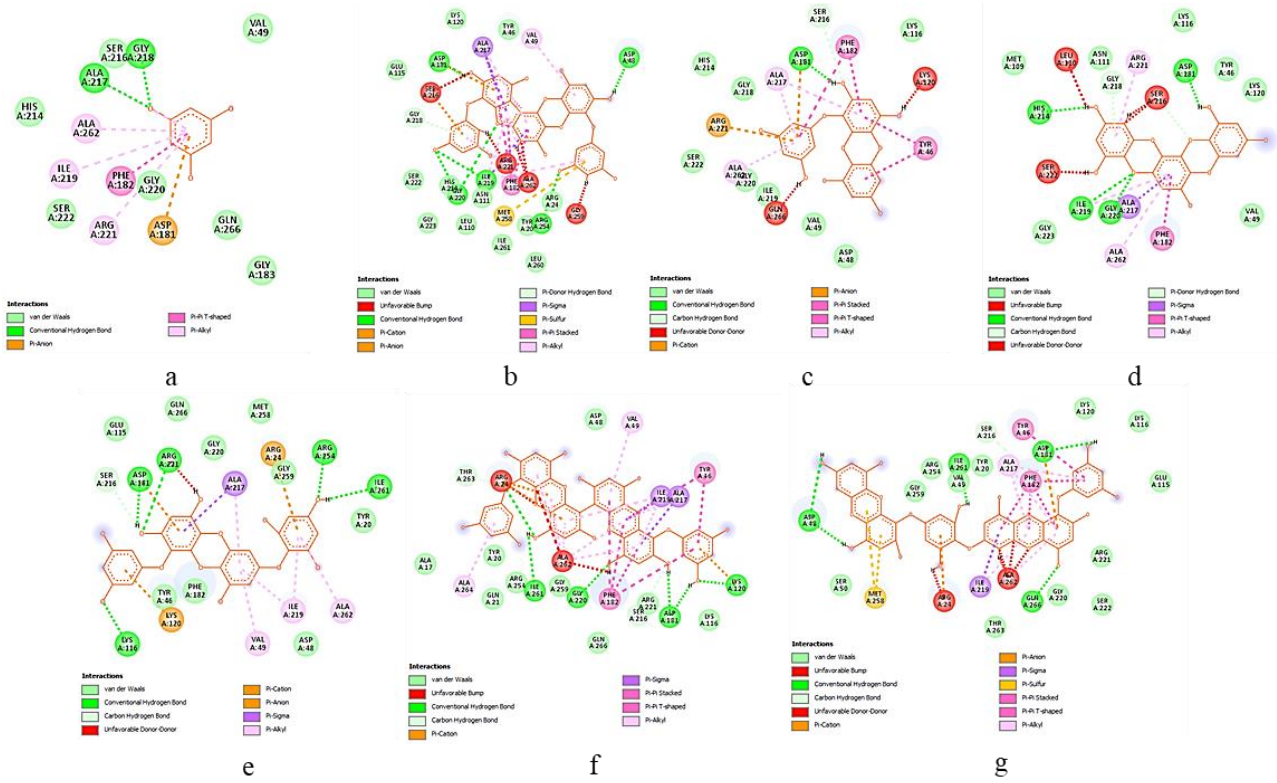
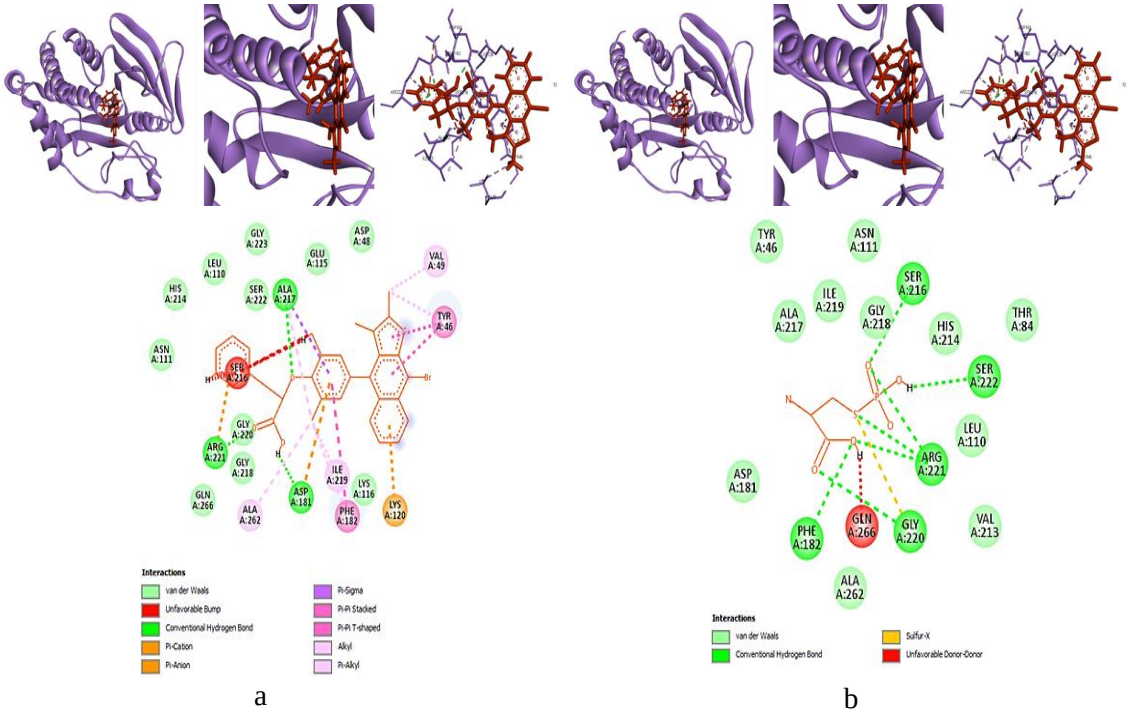


Figure 2. 2D structure of the Phlorotannin Complex Against PTP 1B: a. Phloroglucinol–PTP 1B, b. Phlorofucofuroeckol-A–PTP 1B, c. Eckol–PTP 1B, d. Dioxinodehydroeckol–PTP 1B, e. 7-Phloroeckol–PTP 1B, f. Dieckol–PTP 1B, g. 6,6′-Bieckol–PTP 1B



a b

Figure 3. 3D and 2D Structures of the Control Compound Ertiprotafib: a. and S-phosphocysteine, b. Against PTP 1B

addition, the active compound phlorotannins can be used as a substitute agent for the drug Ertiprotafib and can decrease the drug's side effects.

Ertiprotafib inhibits the PTP 1B's activity by binding to the active site A:Lys120, A:Asp181, A:Ala217, A:Ala262, A:Val49, A:Ile219, A:Tyr46, A:Phe182, A:Arg221, and A:Ser216. The Lys120 residue identified as a bound by Ertiprotafib was also present in the compounds 7-phloroeckol, eckol, and dieckol. The residues Asp181, Ala217, Ala262, and Ile219 are the active sites detected in all phlorotannins and Ertiprotafib. Val49 was detected by the active sites phlorofucofuroeckol-A, 7-phloroeckol, and dieckol. Tyr46 was identified in the active site residues of eckol, dieckol, and 6,6′-bieckol. Arg221 was placed on all active sites of the compound phlorotannins, except dieckol and 6,6′-bieckol. The Phe182 residue was also detected on all active sites of phlorotannin compounds, except compounds phlorofucofuroeckol-A and 7-phloroeckol.

Phe182 residues were detected on all active sites of phlorotannins, except phlorofucofuroeckol-A and 7-phloroeckol compounds. The literature suggests that the Phe182 residue helps close the WPD-loop after binding the substrate to the PTP 1B's active site [10, 11]. The WPD-loop is a major part of the PTP 1B catalytic mechanism, which recruits the phosphotyrosine for the dephosphorylation process [12, 13].

Tyr46 was identified in the active site residues of eckol, dieckol, and 6,6′-bieckol. Research has shown that Tyr46 and Phe182 flank the phenyl ring of the phosphotyrosine substrate and form hydrophobic interactions [14]. The results of other studies have also shown that the presence of Tyr46 and Phe182 results in favorable hydrophobic interactions [15].

The stability parameter of the compound complex was observed by the bond energy: the more negative the bond energy value, the better the stability level between the ligand to the receptor (Table 1). Based on the bond energy values, all compound interactions of the active phlorotannins–PTP 1B produce lower energy than complex S-phosphocysteine–PTP 1B (−266.8 kJ/mol) as a control, except for phloroglucinol–PTP 1B (−208 kJ/mol). Compared with the drug control Ertiprotafib (−322.8 kJ/mol), lower bond energy is owned by phlorofucofuroeckol-A (−370.6 kJ/mol), 7-phloroeckol (−328 kJ/mol), dieckol (−331.8 kJ.mol), and 6.6'-bieckol (−341 kJ/mol). Hence, the lower the bond energy, the stronger the interaction between the compounds with the target protein. The closer to the control value, the higher the potential for the inhibition of the target protein.

ADME prediction. Table 2 presents data for pharmacokinetics of each active compound phlorotannins based on the parameters listed. Phloroglucinol has the highest water solubility compared to the control drug Ertiprotafib and other phlorotannin compounds. In addition, the permeability of phloroglucinol to Caco-2 (epithelial cell colorectal adenocarcinoma in humans) had a value of more than 0.90 and was close to the value of the control drug.

Table 1. Interactions Between the Active Compound Phlorotannins Against PTP 1B

No.	Complex Compound	Binding Energy (kJ/mol)	Bond Type
1.	Phloroglucinol–PTP 1B	−208.0	Hydrogen bond, electrostatic, hydrophobic
2.	Phlorofucofuroeckol-A–PTP 1B	−370.6	Hydrogen bond, electrostatic, hydrophobic, others, unfavorable
3.	Eckol–PTP 1B	−299.8	Hydrogen bond, electrostatic, hydrophobic, unfavorable
4.	Dioxinodehydroeckol–PTP 1B	−270.0	Hydrogen bond, hydrophobic, unfavorable
5.	7-phloroeckol–PTP 1B	−328.0	Hydrogen bond, electrostatic, hydrophobic, unfavorable
6.	Dieckol–PTP 1B	−331.8	Hydrogen bond, electrostatic, hydrogen bond; electrostatic, hydrophobic, unfavorable
7.	6,6′-bieckol–PTP 1B	−341.0	Hydrogen bond, electrostatic, hydrophobic, others, hydrophobic, unfavorable
	Control		
8.	S-phosphocysteine–PTP 1B	−266.8	Hydrogen bond, others unfavorable
9.	Ertiprotafib–PTP 1B	−322.8	Hydrogen bond, electrostatic, hydrophobic, unfavorable

Table 2. Pharmacokinetics of the Active Compound Phlorotannins

Compound	Parameter	Phloroglucinol	Phlorofucofuroeckol-A	Eckol	Dioxinodehydroeckol
Absorption	**Water solubility (log mol/L)**	−1.408	−2.892	−2.899	−2.895
	Caco-2 permeability (log Papp in 10-6 cm/s)	1.102	−0.967	−0.203	−0.441
	Intestinal absorption (% absorbed)	83.549	68.892	67.167	91.311
	P-glycoprotein substrate	No	Yes	Yes	Yes
	P-glycoprotein I inhibitor	No	No	No	No
	P-glycoprotein II inhibitor	No	Yes	Yes	Yes
Distribution	**VDss (log L/kg)**	0.130	−0.218	0.595	−0.856
	Fraction unbound (Fu)	0.713	0.371	0.082	0.101
Metabolism	**CYP3A4 substrate**	No	No	No	No
	CYP1A2 inhibitor	No	Yes	No	Yes
	CYP2C19 inhibitor	No	No	No	Yes
	CYP2C9 inhibitor	No	No	No	Yes
	CYP2D6 inhibitor	No	No	Yes	Yes
	CYP3A4 inhibitor	No	No	No	No
Excretion	**Total clearance (log ml/min/kg)**	0.581	−0.267	0.232	0.428
	Renal OCT2 substrate	No	No	No	No

Table 2. ***Continue***

Compound	Parameter	7-phloroeckol	Dieckol	6,6′-bieckol	Ertiprotafib
Absorption	**Water solubility (log mol/L)**	−2.892	−2.892	−2.892	−2.983
	Caco2 permeability (log Papp in 10-6 cm/s)	−0.69	−0.664	−0.643	1.316
	Intestinal absorption (% absorbed)	68.361	94.013	78.352	100
	P-glycoprotein substrate	Yes	Yes	Yes	Yes
	P-glycoprotein I inhibitor	Yes	No	No	No
	P-glycoprotein II inhibitor	Yes	Yes	Yes	Yes
Distribution	**VDss (log L/kg)**	−0.315	−0.715	−0.200	−1.868
	Fraction unbound (Fu)	0.228	0.362	0.374	0.214
Metabolism	**CYP3A4 substrate**	No	No		No
	CYP1A2 inhibitor	Yes	Yes	Yes	Yes
	CYP2C19 inhibitor	No	No	No	No
	CYP2C9 inhibitor	No	No	No	Yes
	CYP2D6 inhibitor	No	No	No	Yes
	CYP3A4 inhibitor	No	No	No	No
Excretion	**Total clearance (log ml/min/kg)**	0.084	0.021	−0.349	−0.389
	Renal OCT2 substrate	No	No	Yes	No

Hence, the two compounds (phloroglucinol and Ertiprotafib) have a higher absorption of Caco-2 than the other phlorotannins, which are much lower. All compounds can be well absorbed in the intestines because the human intestinal absorption value is above 30%. Phloroglucinol is the only phlorotannins that are not a substrate of P-glycoprotein (P-gp), which means that phlorotannins can mediate the efflux of P-gp and can indirectly reduce the amount of the compound absorbed into the bloodstream. All compounds can act as P-gp inhibitors except phloroglucinol.

The steady-state volume of distribution (VDss) on eckol has a log VDss value >0.45, which means that the compound is the only compound that is widely distributed in body tissues. Meanwhile, other phlorotannins have a log VDss value <−0.15, which means that these compounds are more commonly spread in the blood plasma than in the body tissues. Eckol and dioxinodehydroeckol had a lower fraction unbound (FU) value than the drug control. Hence, the two compounds cannot cross cell membranes or diffuse and the control drug Ertiprotafib, whereas other phlorotannins can cross or diffuse better than the control drug. Next, dioxinodehydroeckol is the only phlorotannins that can penetrate the central nervous system well, although not as well as the control drug Ertiprotafib.

All phlorotannins are not CYP3A4 substrate, which means that phase 1 metabolism through cytochrome P450 enzymes does not occur in phlorotannins. Studies show that phlorotannins are metabolized and absorbed primarily through the colon, and there is a great variation in each individual's metabolic profile [16].

All phlorotannins had a total clearance than the control drug Ertiprotafib. The total clearance is the total ability of the body to clear drugs from the plasma, which is the sum of the renal clearance, liver clearance, and clearance from all other tissues [17]. 6,6′-bieckol is the only compound that can be a renal substrate for the organic cation transporter 2 (OCT2). Therefore, 6,6′-bieckol is not recommended to be taken together with drugs that have OCT2 inhibitors because it can reduce the effectiveness of its antidiabetic. Some examples of drugs with OCT2 inhibitors are cimetidine, trimethoprim, levofloxacin, propranolol, metoprolol, and quinine [18]. In contrast to metformin, some potent OCT2 inhibitor drugs are mediated by antidiabetic drugs, such as trimipramine, trospium chloride, doxepin, and pantoprazole [19].

Drug potential (druglikeness) prediction. The prediction of drug potential, consisting of Lipinski, Veber, Egan, and Bioavailability Score, is listed in Table 3. According

to Lipinski's rules, phloroglucinol, eckol, and dioxinodehydroeckol have the potential to be used as drugs, whereas the other phlorotannins do not have the potential to be used as drugs because they do not comply with Lipinski regulations. Then, based on the rules of Veber and Egan, only phloroglucinol has the potential to become a drug. The highest bioavailability was still owned by the control drug Ertiprotafib, whereas the phlorotannins whose bioavailability was almost close to the control drug were phloroglucinol, eckol, and dioxinodehydroeckol. Based on the obtained data, phloroglucinol has the most potential to become a drug compared to other compounds, although eckol and dioxinodehydroeckol also have this potential.

Of all the tests carried out and previous studies, all the active compounds of phlorotannins show an antidiabetic effect [20]. Of the seven types of phlorotannins, all PTP 1B inhibitory compounds' activity is strong, except for phloroglucinol [21]. Eckol, dieckol, 7-phloroeckol, and phlorofucofuroeckol-A were the most potent PTP 1B inhibitors that were measured based on their IC50 values [5].

Toxicity prediction. As shown in Table 4, the toxicity of each phlorotannins active compound has differences based on the parameters listed. Phloroglucinol, phlorofucofuroeckol-A, eckol, 7-phloroeckol, dieckol, and 6,6′-bieckol did not show mutagenic activity, whereas the compound dioxinodehydroeckol was a potential mutagen as indicated by the positive value of the Ames test. The maximum recommended tolerated dose is a toxic dose limit that can be tolerated in humans and can be used as a guide for the maximum recommended initial dose for drugs in stage 1 clinical trials. A value of 0.477 mg/kg/day signifies nontoxicity. All active compounds of phlorotannins have the potential as human ether-a-go-go gene (hERG) II inhibitors that inhibit potassium channels, except phloroglucinol. Hence, all the compounds can incur the development of acquired long QT syndrome and lead to fatal ventricular arrhythmias, but not phloroglucinol. The phloroglucinol compound's LD50 showed the lowest value compared to the control and other compounds. Hence, in low concentrations, phloroglucinol compounds can kill 50% of rat models. Interestingly, the active compound was less toxic to hepatocyte cells than the control drug Ertiprotafib, so the use of the active compound phlorotannins is safer than the synthetic drug Ertiprotafib. The predicted toxicity class of phloroglucinol and phlorofucofuroeckol-A is class 3. The predicted toxicity class of compounds eckol, dioxinodehydroeckol, 7-phloroeckol, and dieckol is class 4. Meanwhile, the highest predicted toxicity class is that of the 6,6′-bieckol compound, i.e., class 5, which has the same value as the Ertiprotafib control drug. The lower the grade, the smaller the toxic dose until it is fatal if swallowed.

Based on the study results, all phlorotannins do not cause hepatotoxicity. Dieckol from *E. cava* showed low toxicity to human leukemia cells and mouse basophilic leukemia cells [22]. In addition, dieckol is not cytotoxic to the human venous endothelial cells (HUVEC) and promotes the suppression of postprandial blood sugar levels [23]. Furthermore, dieckol significantly inhibits glucose-induced toxicity and can increase antioxidant enzymes, such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx), in high-glucose pretreated insulinoma cells [24]. According to the toxicity test that has been carried out in this study,

Table 3. Phlorotannin Active Compounds' Druglikeness

Compound	Druglikeness			
	Lipinski	**Veber**	**Egan**	**Bioavailability Score**
Phloroglucinol	Yes; 0 Violation	Yes	Yes	0.55
Phlorofucofuroeckol-A	No; 3 violations: MW>500, NorO>10, NHorOH>5	No; 1 violation: TPSA>140	No; 2 violations: WLOGP>5.88, TPSA>131.6	0.17
Eckol	Yes; 1 violation: NHorOH>5	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	0.55
Dioxinodehydroeckol	Yes; 0 violation	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	0.55
7-phloroeckol	No; 2 violations: NorO>10, NHorOH>5	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	0.17
Dieckol	No; 3 violations: MW>500, NorO>10, NHorOH>5	No; 1 violation: TPSA>140	No; 2 violations: WLOGP>5.88, TPSA>131.	0.17
6,6′-bieckol	No; 3 violations: MW>500, NorO>10, NHorOH>5	No; 1 violation: TPSA>140	No; 2 violations: WLOGP>5.88, TPSA>131.6	0.17
Ertiprotafib	No; 2 violations: MW>500, MLOGP>4.15	Yes	No; 1 violation: WLOGP>5.88	0.85

Table 4. Toxicity of the Active Compound Phlorotannins

Parameter	Phloroglucinol	Phlorofuco-furoeckol-A	Eckol	Dioxinode-hydroeckol	7-phloroeckol	Dieckol	6,6′-bieckol	Ertiprotafib
AMES Toxicity	No	No	No	Yes	No	No	No	No
Max tolerated dose (log mg/kg/day)	0.107	0.438	0.476	0.451	0.439	0.438	0.438	0.421
hERG I inhibitor	No	No	No	No	No	No	No	No
hERG II inhibitor	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Oral Rat Acute Toxicity (LD50) (mol/kg)	1.958	2.482	2.584	2.482	2.502	2.482	2.482	2.613
Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)	2.149	5.515	3.094	2.223	4.166	3.949	5.854	-0.288
Hepatotoxicity	No	No	No	No	No	No	No	Yes
Predicted toxicity Class	3	3	4	4	4	4	5	5

dieckol has also show a hepatoprotective effect on ethanol-induced rats [25]. Meanwhile, based on previous studies, apart from having the highest toxicity value, 6,6′-bieckol also has a protective effect on HUVECs under hyperglycemic conditions and against glucose-induced cell damage, such that it can prevent endothelial dysfunction associated with diabetes complications [21, 24]. 6,6′-bieckol can also treat high levels of glucose-induced toxicity in rat insulinoma cells [26].

Conclusion

In the predictive analysis of the relationship between the phlorotannins with PTP 1B, each active compound can bind to PTP 1B in the same binding region as the control. This finding indicates that the active compound phlorotannins have the potential as antidiabetic drugs amd function like drug control. This condition is proven, as phlorotannins–PTP 1B produce lower energy than the complex S-phosphocysteine–PTP 1B (−266.8 kJ/mol) as a control, except for phloroglucinol–PTP 1B (−208 kJ/mol). Compared with the drug control Ertiprotafib (−322.8 kJ/mol), the lower bond energy is owned by phlorofucofuroeckol-A (−370.6 kJ/mol), 7-phloroeckol (−328 kJ/mol), dieckol (−331.8 kJ.mol), and 6.6‘-bieckol (−341 kJ/mol). Moreover, phlorotannins are very well absorbed through the small intestine, and the distribution of most of the active compounds to cell membranes is good than that of eckol and dioxinodehydroeckol. According to Lipinski’s rule, phloroglucinol, eckol, and dioxinodehydroeckol have the potential as drugs. Besides, all active compounds of phlorotannins are nontoxic to hepatocytes compared to the control drug Ertiprotafib. Hence, using the active compound is safer and causes fewer side effects than using the synthetic drug Ertiprotafib. Therefore, phlorotannins can also be used as a substitute agent for the drug Ertiprotafib, thereby reducing the side effect of the drug.

This research is limited to assumptions. Thus, further research is needed, such as molecular dynamics and in vitro and in vivo analysis using various extract doses based on the toxicity tests that can be performed to determine the optimal and toxic dose in experimental animals.

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