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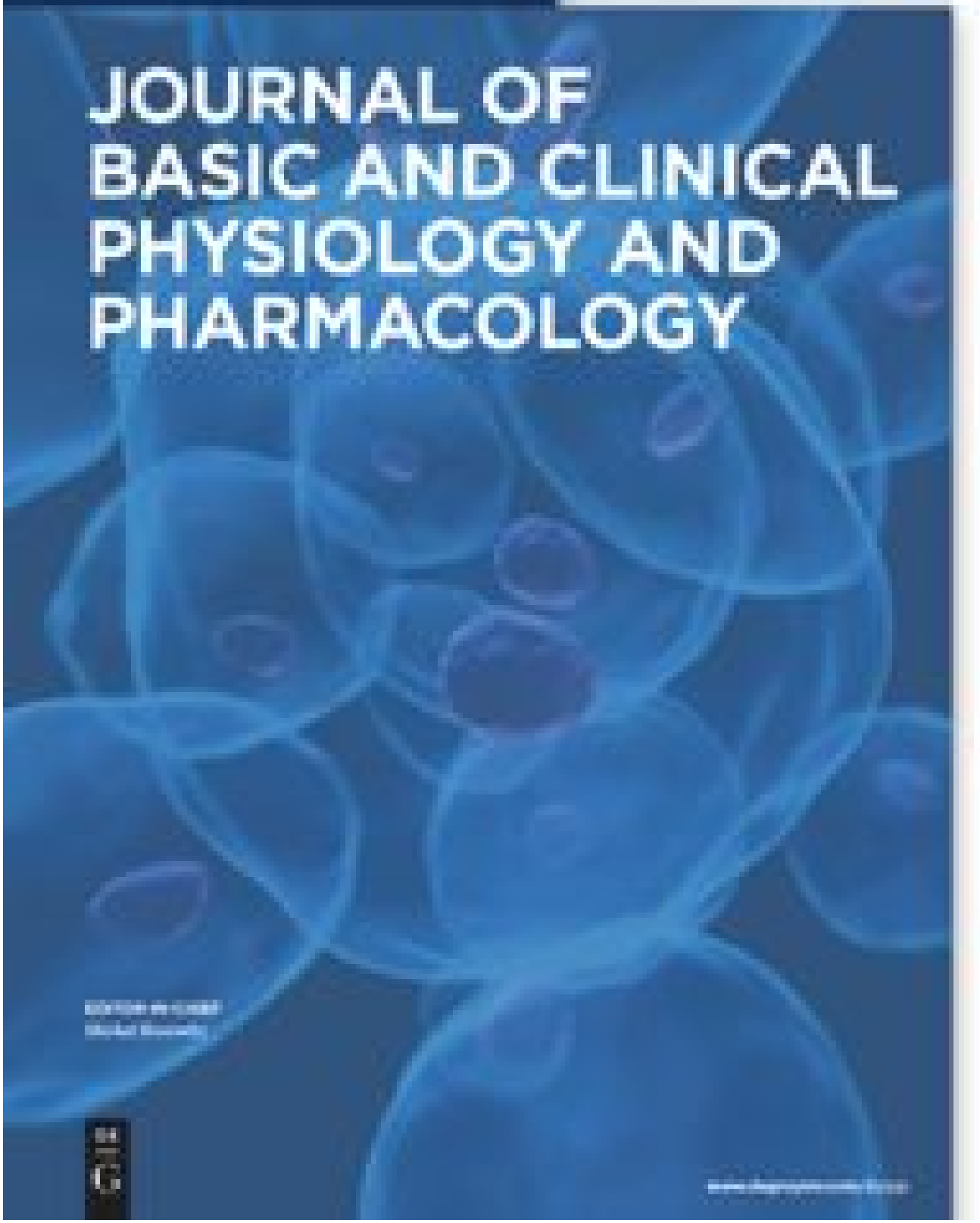

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Shallot skin profilling, computational evaluation of physicochemical properties, ADMET, and molecular docking of its components against P2Y12 receptor

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Abstract

Objectives: Medicinal plants are a source of many compounds that are useful in the pharmaceutical field for novel drug development. Polyphenols and the flavonoid group in plants are known to have several activities, such as relieving cardio vascular disease (CVD). The outer skin of the shallot which is disposed of as waste is known to have an antiplatelet activity which was tested *in vitro* assay. To date, there is no study reported on the ADMET profile and physicochemical properties of the active component of the shallot skins.

Methods: The extraction of shallot skins was conducted by ultrasonic irradiation using ethanol. The phytochemical screenings were carried out by TLC and color reaction. The profiling of its active ingredient was presented by GC-MS, HPLC and spectrophotometry UV–vis. Whereas their physicochemical properties were analyzed by ChemDraw 17.00 program and the ADMET predictions were studied using pkCSM online tool. The MVD program was operated in the docking study on protein P2Y12 (PDB ID 4PXZ).

Results: The extract showed the presence of polyphenol, flavonoids, quercetin, natalensine-3,5-dinitrobenzoate; bis [2-(2-fluorophenyl)-6-fluoroquinolin-4-yl]amine, benzo[a] heptalene, *N*-(trifluoroacetyl) methyl-*N*-deacethyl-colchicine. The ADMET prediction data displayed that the compounds in the extract have good absorption so that they can be used in the oral and transdermal routes. Some components in the extract have lower MDS than clopidogrel.

Conclusions: The ultrasonicated shallot skin extract can be used as additional resources of the active pharmaceutical ingredients and to have the potency to be developed as an oral or transdermal preparation.

Keywords: ADMET; cardiovascular disease; P2Y12 receptor; quercetin; shallot skin profilling; ultrasonic extraction.

Introduction

Cardiac Vascular Disease (CVD), especially coronary heart disease, greatly contribute to the mortality rate across the globe, and patient medical costs continue to increase due to an increase in the number of sufferers [1, 2]. This disease occurs due to impaired blood flow to the myocardium due to platelet aggregation, thrombus, and the accumulation of oxidative damage to Low Density Lipid (LDL) by Reactive Oxygen Species (ROS) [1, 3]. Oxidant stress causes endothelial dysfunction and thrombus formation [4].

Drugs used to treat coronary heart disease are thrombolytic, antiplatelets and several antioxidants [5, 6]. Although they can treat coronary heart conditions due to thromboembolism, these drugs also have undesirable side effects such as intracranial bleeding, nausea, dyspnea, and it was reported that the patient had resistance to aspirin as an antiplatelet [7, 8]. Therefore, alternative therapies are needed to overcome the above problems with mild side effects.

Medicinal plants are a source of many chemical compounds that are useful in the pharmaceutical field for novel drug development, including polyphenols, the flavonoid class. The flavonoid group are known to have several activities, such as antibacterial and antioxidant [9, 10]. One of the natural ingredients that is widely used in daily food is shallots. Shallots have the active compound i.e. polyphenol quercetin as an antibacterial [11]. Not only the tuber part of the shallot, the outer skin of the shallot which is disposed of as waste is also known to have anti-inflammatory [12]

***Corresponding author: Juni Ekowati**, Department of Pharmaceutical Sciences, Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia, Phone: +62 81332041503, E-mail: juni-e@ff.unair.ac.id
Kholidah Febriani, Itsna N. A. Yaqin, Adinda A. Wulandari, Indra H. Mulya, Kholis A. Nofianti and Achmad Syahrani, Department of Pharmaceutical Sciences, Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia

and antimicrobial activity [13, 14]. It was also reported that there is antioxidant activity of the ethanolic extract from shallot skins using the 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) method [15]. Apart from being antibacterial and antioxidant, the activity of shallot extract as an antiplatelet which was tested *in vitro* has also been revealed by Ro et al. [16]. These things show that the shallot skins has the potency as an active pharmaceutical ingredient (API).

Beside the activity, prospective drug compounds also need to be investigated regarding their physicochemical properties and pharmacokinetic profile, including absorption, distribution, metabolism, and excretion as well as its toxicity (hereinafter referred to as ADMET) to humans [17]. The pharmacokinetic profile of a drug could been influenced by the physicochemical properties [18]. Lipnski et al. has formulated several criteria regarding the physical and chemical properties of compounds that can demonstrate its oral bioavalability, consisting of: the ability to accept and donate hydrogen, molecular weight, and log p [19].

However, until now, there no research on the physicochemical and pharmacokinetics (ADMET) of the active ingredients of shallot skins. The effects of administering the extract on the gastrointestinal tract also need to be studied to ensure its safety in oral use. Therefore, this study aims to find out the component of shallot skin, its physicochemical properties prediction, and its pharmacokinetics (ADMET) prediction.

Pharmacokinetic profile analysis (ADMET) *in silico* is able to be conducted with the help of the online pkCSM program [20]. Prediction with the online pkCSM program has advantages over other software such as SwissADME, since there are more pharmacokinetic parameters that can be predicted with the online pkCSM program [21, 22] The greater number of parameters will have an impact on the broader information obtained to support the next drug development process.

Based on the research of Ro et al. [16] which states that shallot skins extract has antiplatelet activity *in vitro*, this study also evaluated the inhibition mechanism of the P2Y12 receptor by *in silico* test (PDB ID 4pxz). P2Y12 is a main receptor and the distinctive P2 goal for clinically allowed antiplatelet drugs (herein named as P2Y12 inhibitors) [17, 23].

Materials and methods

The waste from shallot skins obtained from traditional markets is collected, washed, then dried at room temperature, and powdered using a blender. Previously, the species of shallot skin were examined at the Materia Medica Batu institute, and it was found that the shallot species was *Allium cepa* L. Ethanol p.a. (Merck, Germany) was used as solvent of extraction.

Extraction

The powder then extracted in ethanol using the ultrasonic method. First, 80 g of shallot skin powder soaked in 500 mL Erlenmeyer with 350 mL 96% ethanol, then performed ultrasonic at high power and temperature at 40 °C for 30 min. The extraction product is then filtered using a Buchner funnel under vacuum; the filtrate is accumulated in a different Erlenmeyer. Second, the extracted pulp was put back into the Erlenmeyer 500 mL and added with 300 mL of 96% ethanol. The same process then carried out like the previous process. The extracted filtrate collected and carried out at a rotary evaporator. This ultrasonic extraction was repeated 14 times (until the filtrate did not react with $FeCl_3$, this is indicated by the solution remains clear).

Phytochemical screening

Screening of flavonoid content was carried out by Thin layer Chromatography (TLC) method, using stationary phase silica gel GF254, the mobile phase butanol-acetic acid glacial-water (4:1:5) and ammonia vapor was used as color reagent. While the polyphenol group was detected by solution $FeCl_3$ 2%.

Chromatographic profile

Examination of chemical compounds carried out by Gas Chromatography – Mass Spectrometry (GC–MS). The sample was weighed 100 mg, dissolved 2 mL of p.a. ethanol, then vortexed for 2 min, centrifuged at 3,000 rpm for 5 min. The filtrate was injected into 0.1 µL GC–MS, under optimum conditions. The instrument used in this study was Agilent 6980N Network GC system with auto sampler with detector Agilent 5973 inert MSD Inlet split 1/100. Run at a temperature of 250 °C, 50 °C programmed oven for 5 min, an increase of 10 °C every minute to 280 °C for 15 min, the rate in the column is 1 mL/min constant, Aux is 250 °C, MS Quad 150 °C, MS Source 230 °C, solvent delay 0 min, Wiley library version 7.0, and sample injection volume is 0.1 µL.

Polyphenol assay

Polyphenol content test was carried out by spectrophotometric method. A standard solution of Gallic acid was made with a level of 5–25 ppm. Each with a pipette of 1.0 mL put into the vial, added 0.5 mL of Folin–Ciocalteu, left for 5 min, and then added 2 mL of 10% sodium carbonate solution. After that the absorbance was measured at λ = 770 nm. Sample preparation was carried out by weighing 50 mg of the sample, dissolved in 50 mL of ethanol, then pipetting 1 and 10 mL, the dilution of the sample was piped 1.0 mL and then put into the vial. Furthermore, 0.5 mL of Folin–Ciocalteu was added, the mixture was 5 min, then added 2 mL of 10% sodium carbonate solution, the mixture was added 10 min before measuring the absorbance (at λ = 765 nm).

Quercetin content assay

Quercetin content test was carried out by High Pressure Liquid Chromatography (HPLC). Qualitative analysis was performed by comparing the identical retention time of the sample solution chromatogram with the quercetin standard solution chromatogram at the

same HPLC conditions. Quercetin standards were made of a standard solution of 50 ppm, pipette 0.6, 0.8, 1, and 1.2 mL, each put into a 5 mL volumetric flask, then diluted with solvent to the mark line, so that the concentrations solutions are 6, 8, 10, and 12 ppm. The ethanol extract was filtered by a 0.45 μm filter membrane and sonicator for 20 min. After that, each solution was injected into the HPLC system at a certain mobile phase and flow rate. The chromatogram is recorded and a calibration curve is made between the area of the peak and the concentration. From the measurement results, the area obtained is recorded, then the levels are calculated using a calibration curve (linear regression equation): $y = a + bx$.

Physicochemical and ADMET prediction

Physicochemical prediction was carried out by ChemDraw version 17.00, while the ADMET prediction was carried out by the *online* program, pkCSM that can be accessed from http://biosig.unimelb.edu.au/pkcsm/prediction. These test was ran in ASUS A407UA BV032T Intel core i-3 7th-7020U 2.30 GHz, Windows 10 64 bit.

Docking study

The docking study was carried out using Molegro Virtual Docker program version 5.5. (Molegro ApS). Some of the steps involved in Molecular Docking program were: obtaining the receptor, ligand preparation, method validation, and docking studies. The receptor used in this study was the P_2Y_{12} receptor, which can been downloaded from the Protein Data Bank (http://www.rcsb.org). This P_2Y_{12} receptor has the code for PDB 4PXZ with 6AD_1201[A] as native ligand. The ligands that used in this study were the compounds obtained from shallot skins that was known from GC–MS and quercetin test. The ligands structure drew in ChemDraw 2D version 17.00 and copying into ChemDraw3D version 17.00 to get the 3D structure. The best conformation was determined from MMFF94, and then saved in sybil.mol2 extension. The docking process, native ligands, namely 6AD_1201[A] for P_2Y_{12} was redocked to the suitable binding site [22]. The results of the docking studies could be detected visually by comparing the structure of the ligands and receptor P_2Y_{12} (6AD_1202[A]) in the binding site. This resulted in the interaction energy between ligand and receptor was then called as MolDock scores (MDS). The minimum energy denotes the best binding pose between the functional moiety of the ligand and the amino acid residue of the receptor [17].

Results

Extraction

The extraction of shallot skin in 96% ethanol by ultrasonic method produces as much as 13.149 g of thick extract. The screening phytochemical extract showed that the extract contained flavonoid and polyphenol compounds. The plate TLC showed the black spot, which is product reaction of phenolic moiety with $FeCl_3$. Whereas that plate showed yellowish spot which showed flavonoid content.

Chromatographic profile

The results of examination of chemical compounds by GC–MS show in Table 1, which show that Bis[2-(2-fluorophenyl)-6-fluoroquinolin-4-yl]amine has the highest percentage. The measurements were also carried out to determine the presence and levels of quercetin and polyphenol (which using Gallic acid as the standard) in the ethanol extract of shallot skins as shown in Table 2.

Physicochemical and ADMET prediction

The *in silico* test was carried out to calculate the physicochemical and pharmacokinetic properties of the compounds contained in the shallot skins as shown in Table 3. The molecular weight ranges from 204.272 to 495.479. Log p value, which is a lipophilicity parameter, ranges from 1.988 to 8.417. The bond rotation, HBA, and HBD respectively ranges from 0 (Benzo[a]heptalene) until 7 (*N*-(trifluoroacetyl)methyl-*N*-deacethyl-Colchicine and Querc-etin), from 0 (Benzo[a]heptalene) until 10 (Natalensine, 3,5-dinitrobenzoate), and from 0 (Benzo[a]heptalene) until 5 (Quercetin).

Docking study

Figure 1 shows P2Y12 (PDB ID: 4PXZ) with the ligand reference: 6AD-1201. The docking study was carried out in cavity 2 Vol 74.752. While Figure 2 shows the interaction between ligands and amino acids at P_2Y_{12} receptors.

Table 1: Examination of chemical compounds by GC–MS.

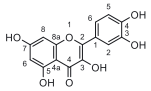
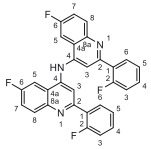
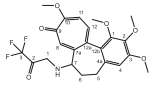
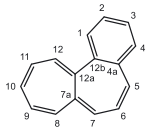
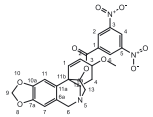
RT	Compound name	%Normality	Qual
28.34	Natalensine, 3,5-dinitrobenzoate	13.43%	30
28.85 and 33.05	Bis[2-(2-fluorophenyl)-6-fluoroquinolin-4-yl]amine	36.90%	35
29.13	Benzo[a]heptalene	17.43%	95
29.30	*N*-(trifluoroacetyl)methyl-*N*-deacethyl-colchicine	32.23%	35

Table 2: Quercetin and polyphenol content in extract.

Content	Quantity in extract Mean %(b/b) ± RPD
Quercetin	4.61 ± 2.43
Polyphenol	11.14 ± 5.12

RPD: relative percent difference.

Table 3: Physicochemical and pharmacokinetic prediction.

Compound	Structure	MW	Boiling point, K	Melting point, K	Log p	Bond rotation	HBA	HBD	PSA	Absorption	
										Water solubility	Intestinal absorption
Quercetin		302.238	1135.37	970.62	1.988	1	7	5	122.108	−2.925	77.207
Bis[2-(2-fluorophenyl)-6-fluoroquinolin-4-yl] amine		495.479	1225.17	896.7	8.417	4	3	1	208.617	−3.577	93.87
N-(trifluoroacetyl) methyl-*N*-deacethyl-colchicine		467.44	1076.21	754.77	3.4565	7	7	1	187.966	−3.781	93.15
Benzo[a]heptalene		204.272	643	367.64	2.24	0	0	0	94.932	−3.691	99.286
Natalensine, 3,5-dinitrobenzoate		495.444	–	–	2.8678	5	10	0	203.836	−4.896	94.254

Compound	Absorption		Distribution			Metabolism		Excretion	Toxicity		
	Skin permeability	Caco-2 permeability	VDss (human)	BBB permeability	CNS permeability	CYP2D6 substrate	CYP3A4 substrate	Total clearance	AMES toxicity	Hepato toxicity	LD50
Quercetin	−2.735	−0.229	1.559	−1.098	−3.065	No	No	0.407	No	No	2.471
Bis[2-(2-fluorophenyl)-6-fluoroquinolin-4-yl] amine	−2.735	1.165	−0.826	0.343	−0.819	No	Yes	−0.275	No	Yes	3.335
N-(trifluoroacetyl) methyl-*N*-deacethyl-colchicine	−2.716	1.139	0.833	−1.231	−3.21	No	Yes	0.479	No	Yes	2.992
Benzo[a]heptalene	−1.645	1.539	0.207	0.619	−1.986	No	Yes	0.205	No	No	1.573
Natalensine, 3,5-dinitrobenzoate	−2.737	−0.006	0.235	−0.891	−2.55	No	Yes	0.489	Yes	Yes	2.252

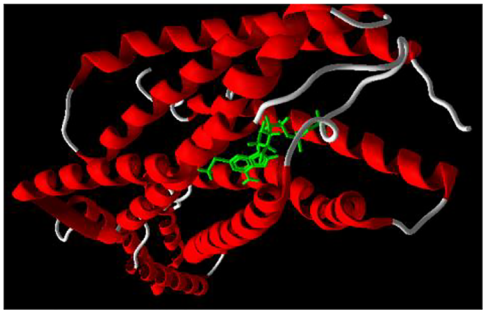


Figure 1: P_2Y_{12} receptor with PDB: ID 4PXZ by which the binding site of the reference ligand and protein will be occupied by the test compounds.

Table 4 revealed the docking results of all tested compounds, ((2R, 3S, 4R, 5R)-5-(6-amino-2-(methylthio)-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl) methyltrihy-drogen diphosphate against P_2Y_{12} receptor. Clopidogrel, Quercetin and Bis[2-(2-fluorophenyl)-6-fluoroquinolin-4-yl]amine. Quercetin and Bis[2-(2-fluorophenyl)-6-fluoroquinolin-4-yl]amine has the similarity amino acid with ((2R, 3S, 4R, 5R)-5-(6-amino-2-(methylthio)-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl trihydrogen diphosphate or Clopidogrel.

Discussion

The outer skins of shallot have known to have anti-inflammatory [12], antimicrobial activity [13, 14] and antioxidant activity [15]. Apart from being antibacterial and antioxidant, the activity of shallot extract as an antiplatelet test also tested *in vitro* by Ro et al. [16]. This study

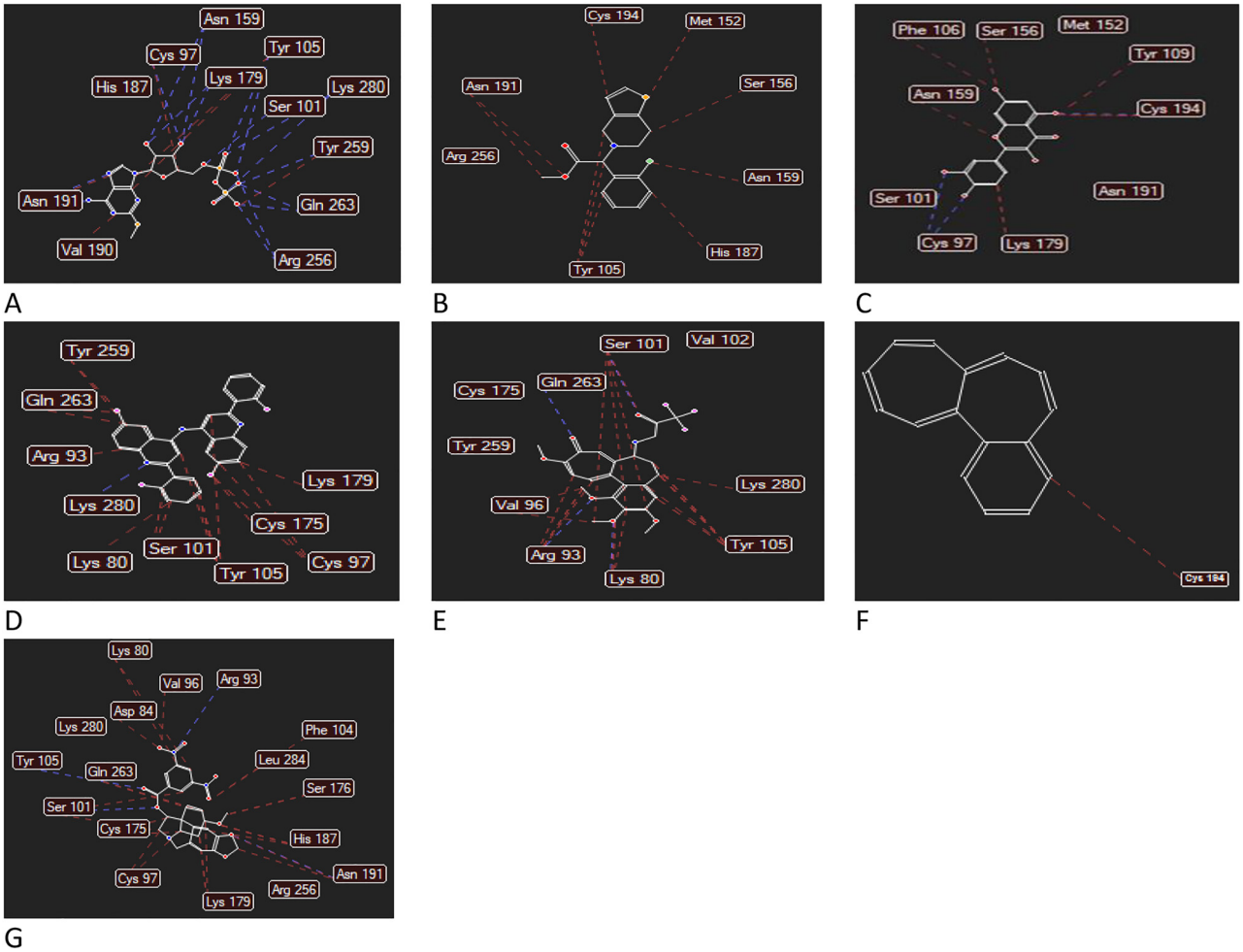


Figure 2: Map of the interaction between shallot skins compound and P_2Y_{12} receptor: (A) ((2R, 3S, 4R, 5R)-5-(6-amino-2-(methylthio)-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl trihydrogen diphosphate, (B) Clopidogrel, (C) Quercetin, (D) Bis[2-(2-fluorophenyl)-6-fluoroquinolin-4-yl]amine, (E) *N*-(trifluoroacetyl)methyl-*N*-deacethyl-Colchicine, (F) Benzo[a]heptalene, and (G) Natalensine, 3,5-dinitrobenzoate.

Table 4: Results of the docking of the test ligand at the binding site of P2Y12 receptor.

Compound name	MDS	Amino acid
((2R, 3S, 4R, 5R)-5-(6-amino-2-(methylthio)-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl trihydrogen diphosphate	−157.334	Arg 256, Asn 159, Asn 191, Cys 97, Gln 263, His 187, Lys 179, Lys 280, Ser 101, Tyr 105, Tyr 259, Val 190
Clopidogrel	−128.010	Arg 256, Asn 159, Asn 191, Cys 194, His 187 Met 152, Ser 156, Tyr 105
Quercetin	−116.863	Asn 159, Asn 191, Cys 97, Cys 194, Lys 179, Met 152, Phe 106, Ser 101, Ser 156, Tyr 109
Bis[2-(2-fluorophenyl)-6-fluoroquinolin-4-yl]amine	−157.041	Arg 93, Cys 97, Cys 175, Gln 263, Lys 80, Lys 179, Lys 280, Ser 101, Tyr 105, Tyr 259
N-(trifluoroacetyl)methyl-*N*-deacethyl-colchicine	−122.252	Arg 93, Cys 175, Gln 263, Lys 80, Lys 280, Ser 101, Tyr 105, Tyr 259, Val 96, Val 102
Benzo[a]heptalene	−101.726	Cys 194
Natalensine, 3,5-dinitrobenzoate	−150.457	Arg 93, Arg 256, Asn 191, Asp 84, Cys 97, Cys 175, Gln 263, His 187, Leu 284, Lys 80, Lys 179, Lys 280, Phe 104,Ser 105, Tyr 105, Val 96

was conducted to determine the benefits of domestic waste shallot skins in the provision of raw materials for Active Pharmaceutical Ingredient.

In this study, the extraction of shallot skins carried out by ultrasonic methods, which the ultrasonic waves were emitted by passing through the medium conducted the waves by inducing vibrational motion of the molecules. The distance between molecules can vary to be closer or farther as the result of the oscillatory motion of the molecules. If the ultrasonic waves in the medium become more intense, a point will be reached where the intramolecular force of the fluid cannot maintain its molecular structure intact. As a result, the molecular structure of the liquid will break down and a cavity is formed [24].

Cavitation is a mechanical activation process that removes the attraction between molecules in the liquid. Once formed, the tiny air bubbles in the cavity will absorb energy from the ultrasonic waves and make the cavity bigger. As the cavity got bigger, the air bubbles inside could no longer absorb ultrasonic energy. Finally, the fluid around the cavity will enter and break the air cavity. The physical characteristic of the irradiated mixture are vital for the cavitation efficiency, and also for the appropriate transfer of acoustic energy to reactants [25–27].

The ultrasonic profiling using the GC-MS method on shallot skin extract (Table 1) showed that the content of Natalensine-3,5-dinitrobenzoate was 13.43%; Bis[2-(2-fluorophenyl)-6-fluoroquinolin-4-yl]amine as much as 36.90%, Benzo[a]heptalene as much as 17.43% and *N*-(trifluoroacetyl)methyl-*N*-deacethyl-Colchicine as much as 32.23%.

Jose et al. [28] stated that the phenyl ring and three methoxyl groups of the colchicine derivative contribute additives to the binding strength of colchicine and its analogues with tubulin, which will affect cancer. Kaivan et al. [29] stated, the use of colchicine for short-term myocardial infarction would reduce the size of the infarction compared to placebo. From this, it could been seen that shallot skin has great potential as API in the treatment of cancer.

Healthy food contain high levels of natural phenols in fruits, vegetables, cereals, tea, and coffee. Fruits such as grapes, apples, pears, cherries, and berries contain up to 200–300 mg of polyphenols per 100 g of fresh weight (0.2–0.3% w/w) [30]. Literatures reported the biological activities of polyphenols such as antioxidants, antibacterial, antineoplastic, antithrombotic, and vasodilating activities [31].

One example of phenolic compound is ferulic acid, which used as antithrombolysis. ADP-induced platelet aggregation test shows that the stronger antithrombolysis activity is attributable to its moiety [32, 33]. Therefore, further research on polyphenols as antithrombolysis is necessary. In this research, extraction of shallot skin, which carried out ultrasonic, had the amount of polyphenols of 11.14% ± 5.12% w/w in the extract.

In relation to the activity of flavonoids as antiplatelet, structure-activity relationship analysis showed that antiaggregation activity of flavonoids are highly rely on the C-ring structure that represent the compounds class. If double bond is present between C2 and C3, it increases antiaggregation activity of flavonoids in case of non-methylated flavonoids. Most active flavonoids possess hydroxyl group at the position 6. Methylation of rings A and B decreases antiplatelet activity [34]. Flavonoid have several mechanisms of action such as change of bilayer function, change in ROS concentrations and oxidative stress, change of intracellular Ca^{2+} concentration, inhibition of enzymes

(phospholipase C, cAMP phosphodiesterase, cyclo-oxygenase, thromboxane A2 synthase) [35].

Quercetin which is usually found in the food consumed, scientifically reported to have anticancer, antiviral, and antimicrobial activity. The use of quercetin is able to decrease CVD risk, LDL (plasma low-density lipoprotein), hypertension, and risk of ischemic heart disease. Its antiplatelet activity also indicated from the ability to inhibit platelet aggregation upon ex vivo post-supplementation and *in vitro* addition [36].

The absorption of active ingredients in the gastrointestinal tract is affected by the physicochemical characteristic of the drug, the dosage form used, and the anatomy and physiology of the absorption site [37]. Passive diffusion is influenced by the size and shape of the molecule, the rate of ionization, and the solubility of a drug in fat. Meanwhile, active ingredients that are weakly alkaline will be absorbed at a more alkaline pH, namely in the small intestine [38].

Predicting the solubility of active ingredients in water significantly contribute to the drug absorption after oral administration and is a consideration in parenteral drug administration. This is useful in the manipulating and testing process in the drug design and development process and is crucial for the bioavailability of drugs in the blood [39]. The ADMET profile of a drug is also related to its physicochemical properties [40, 41]. In Table 3, there are various parameters of physicochemical properties, it is known that the water solubility of Quercetin is 2.925×10^{-4} mol/L; Bis [2-(2-fluorophenyl)-6-fluoroquinolin-4-yl]amine is 3.577×10^{-4} mol/L; *N*-(trifluoroacetyl)methyl-*N*-deacethyl-colchicine is 3.781×10^{-4} mol/L; Benzo[a] heptalene is 3.691×10^{-4} mol/L, and Natalensine, 3,5-dinitrobenzoate is $4{,}896 \times 10^{-4}$ mol/L.

The greater the solubility of the drug in fat (log p), the higher the absorption of the drug into the body's membrane. However, the drug must still be slightly hydrophilic in order for extracellular fluids to be transported and to be distributed throughout the body [42]. Based on Lipinski's law, log p of the active ingredients in the extract, apart from Bis[2-(2-fluorophenyl)-6-fluoroquinolin-4-yl]amine, all of which meet these requirements. Related to Rule of Five [19], the compound Bis [2-(2-fluorophenyl)-6-fluoroquinolin-4-yl] amine is a compound that meets these criteria because the number of hydrogen bond donors (HBD) of each compound <5 and number of hydrogen bond acceptors (HBA) of each compound <10.

tPSA is a molecular descriptor as a parameter for intestinal absorption and drug penetration into the blood brain barrier [43]. From Table 3 It is known that two compounds from shallot skin extract, namely Quercetin and Benzo[a]heptalene, have tPSA values <140 Å. So, that compounds meet Veber's law requirements. Caco-2 permeability is an absorption model that uses monolayer Caco-2 cells as an *in vitro* model predicting the absorption of an orally administered drug. [20]. The compounds in the shallot skins have good permeability apart from 3,5-dinitrobenzoate-Natalensine, this indicates that the compounds in the shallot skins have the potency to be used orally and also have the potential if used through the transdermal route.

The volume of distribution (VDss) is the theoretical the volume by which the drug is dissolved in the body. The high VDss indicates that the majority of the drug is in the tissue [20]. The compounds in the shallot skins are predicted to have different VDss values so that some of the shallot skins compounds will survive in the blood vessels and most of them in the tissues, a good antiplatelet compound is expected more distributed in blood vessels than in tissues.

The drug ability to permeate the Central Nervous System (CNS) was calculated as blood-brain permeability (logPS), which compounds with log pS>−2 are considered to have access on CNS, while compounds with logPS<−3 are unable to penetrate [20]. Of the five test compounds, Quercetin and *N*-(trifluoroacetyl) methyl-*N*-deacethyl-colchicine had a logPS value <−3 meaning the compound was predicted not to permeate the central nervous system. Meanwhile, the other three compounds had a logPS value >−2, which means that the test compounds were predicted to penetrate the central nervous system.

CYP450 substrates, namely CYP2D6 and CYP3A4. are important to identify because CYP450 inhibitors can dramatically alter the pharmacokinetics of drugs metabolized by CYP450 [20]. It was found that apart from Quercetin, the test compound became a CYP3A4 substrate, whereas for CYP2D6, the five compounds did not become a substrate for CYP2D6.

Total clearance is related to bioavailability, and it is important to determine the dosage level to reach a steady-state concentration. Total clearances are expressed in logs (mL/min/kg) [20]. The test results showed that the five test compounds had a total clearance value stated in logs (mL/min/kg) of −0.275 to 0.489.

Toxicity is a pharmacokinetic parameter that is important to determine before designing a drug in order to create a drug that is not only effective and of good quality, but also safe to use. Many compounds can cause hepatotoxicity such as certain drugs, laboratory chemicals and some of herbal medicines [44]. In the shallot skins extract, it is known that Quercetin and Benzo[a]heptalene compounds are not hepatotoxic. Rat Oral Acute Toxicity (LD50) is the amount of compound given at once that can cause

the death of 50% of a group of test animals (mol/kg) [20]. The five test compounds have an LD50 value between 1.573 and 3.335.

Prediction of antiplatelet activity was carried out at the P1Y12 receptor, a G1-protein on platelet membrane surface receptors. It stimulated adenylyl cyclase inhibition and intracellular calcium mobilization [45, 46]. The first generation of P2Y12 receptor inhibitors is the thienopyridine ticlopidine class, which has the side effect of neutropenia. The second generation is the clopidrogel, which is highly metabolized by the CYP450 enzyme [47].

Based on the *in silico* test against the P_2Y_{12} receptor, it is known that, quercetin and Bis[2-(2-fluorophenyl)-6-fluoroquinolin-4-yl]amine has amino acids similar to ((2R, 3S, 4R, 5R)-5-(6-amino-2-(methylthio)-9H-purine-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyltri-hydrogen dip hosphate or clopidogrel, which used as standard. Bis[2-(2-fluorophenyl)-6-fluoroquinolin-4-yl]amine has an MDS value that is close to the standard, whereas quercetin although it has a greater MDS value than the standard, so that its binding ability is smaller, it still does not eliminate the possibility that quercetin can be used against the P_2Y_{12} receptor as antiplatelet. After going through the *in silico* test phase, the shallot skins extract content should be tested *in vivo*. It was concluded that the ultrasonic shallot skin extract can be used as new source of the active pharmaceutical ingredient and are predicted to have the potency as antiplatelet in an oral or transdermal preparation.

Conclusions

The ultrasonic shallot skin extract can be used as new source of the active ingredient for drug development and are predicted to have the potency to be developed as an oral or transdermal preparation.

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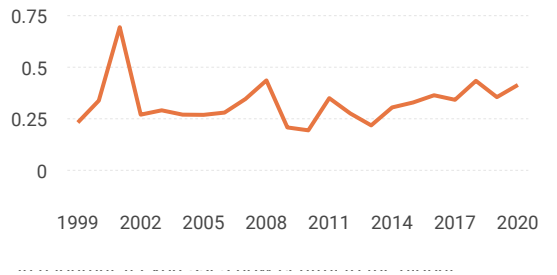

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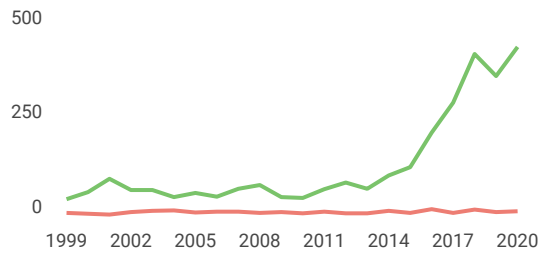

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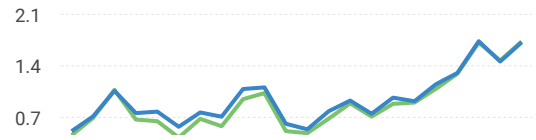

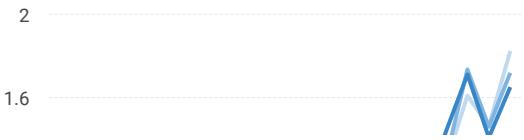

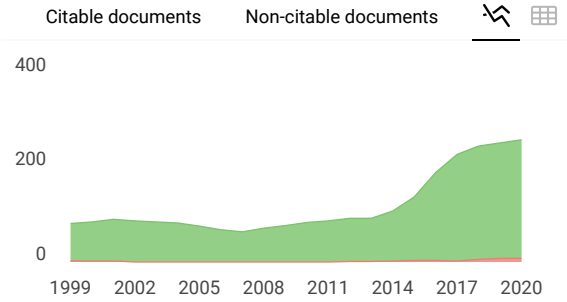

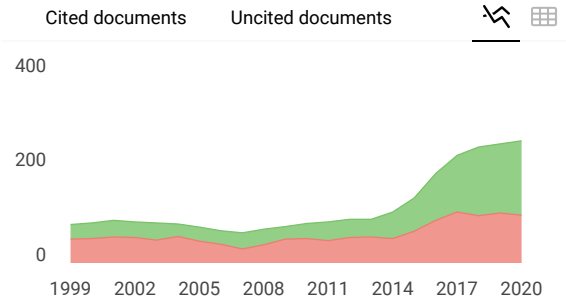

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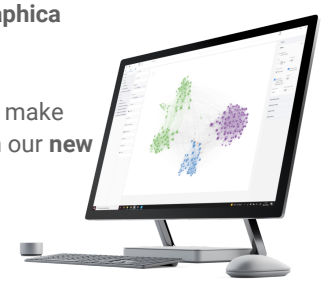

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