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Original Articles

Cost of illness of diabetes mellitus in Indonesia: a systematic review
Yohana Febriani Putri Peu Patty, Mufarrihah, Yunita Nita
Page range: 285–295

Social media health interventions to improve diabetes mellitus patient outcome: a systematic review
Riza Alfian, Umi Athiyah, Yunita Nita
Page range: 297–304

Developing pharmacokinetics–pharmacodynamics model of valproic acid syrup based on prediction of population pharmacokinetics parameter and seizure frequency in Indonesian pediatric epilepsy outpatients
I Komang Prawira Nata Nugraha, Anita Purnamayanti, I Gusti Ngurah Made Suwarba, Nani Parfati
Page range: 305–311

Acetylcholinesterase inhibitory activity of extract and fractions from the root of Rauvolfia serpentina(L.) Bth.ex Kurz
Suciati, Debora Poerwantoro, Aty Widyawaruyanti, Kornkanok Ingkaninan
Page range: 313–317
Green tea and its active compound epigallocatechin-3-gallate (EGCG) inhibit neuronal apoptosis in a middle cerebral artery occlusion (MCAO) model
Abdulloh Machin, Imam Susilo, Djoko A. Purwanto
Page range: 319–325

The effects of quercetin on nicotine-induced reward effects in mice
Mahardian Rahmadi, Dian Suasana, Silvy Restuning Laillis, Dinda Monika Nusantara Ratri, Chrismawan Ardianto
Page range: 327–333

Resveratrol ameliorates physical and psychological stress-induced depressive-like behavior
Chrismawan Ardianto, Aniek Setiya Budiatin, I Nengah Budi Sumartha, Nurrahmi Nurrahmi, Mahardian Rahmadi, Junaidi Khotib
Page range: 335–340

Translation and cross-cultural adaption of an instrument measuring patient’s well-being under treatment for schizophrenia
Julaeha Julaeha, Umi Athiyah, Margarita Maria Maramis, Agus Sugianto, Andi Hermansyah
Page range: 341–347

Quercetin promotes behavioral recovery and biomolecular changes of melanocortin-4 receptor in mice with ischemic stroke
Tuhfatul Ulya, Chrismawan Ardianto, Putri Anggreini, Aniek Setiya Budiatin, Dwi Setyawan, Junaidi Khotib
Page range: 349–355

Knowledge and attitudes of healthcare professionals on prescribing errors
Desak Ketut Ernawati, Ida Ayu Alit Widhiartini, Endang Budiarti
Page range: 357–362

Inhibition of Ras and STAT3 activity of 4-((tert-butyl)-N-carbamoylbenzamide as antiproliferative agent in HER2-expressing breast cancer cells
Aguslina Kirtishanti, Siswandono Siswodihardjo, I Ketut Sudiana, Desak G. A. Suprabawati, Aristika Dinaryanti
Page range: 363–371

Predicting the molecular mechanism of glucosamine in accelerating bone defect repair by stimulating osteogenic proteins
Maria Apriliani Gani, Ahmad Dzulfikri Nurhan, Aniek Setiya Budiatin, Siswandono Siswodihardjo, Junaidi Khotib
Page range: 373–377
Larvicidal toxicity and parasporal inclusion of native *Bacillus thuringiensis* BK5.2 against *Aedes aegypti*
Salamun, Fatimah, Ahmad Fauzi, Seling N. Praduwana, Ni’matuzahroh
Page range: 379-384

Synthesis, ADMET predictions, molecular docking studies, and *in-vitro* anticancer activity of some benzoxazines against A549 human lung cancer cells
Melanny Ika Sulistiyowaty, Retno Widyowati, Galih Satrio Putra, Tutuk Budiati, Katsuyoshi Matsunami
Page range: 385-392

Thymoquinone and its derivatives against breast cancer with HER2 positive: *in silico* studies of ADMET, docking and QSPR
Adinda Adelia Wulandari, Achmad Aziz Choiri, Fitria, Tri Widiandani
Page range: 393-401

Assessment of patient understanding of their conventional cardiac medicines and herbal prepared/derived products: preliminary survey and interviews with selected community-dwelling elderly patients in the Philippines
Jay P. Jazul, Trisha Michaela G. Arciga, Mary Angelie C. Ante, Danavin Gwyneth B. Berlin, Loise Francoise L. Ravana, Samantha A. Reyes, Jashanjit Singh
Page range: 403-413

The development and validation of the health belief model questionnaire for measuring factors affecting adherence in the elderly with hypertension
Rodhiyatul Fithri, Umi Athiyah, Elida Zairina
Page range: 415-419

Analysis of the side effect of QTc interval prolongation in the bedaquiline regimen in drug resistant tuberculosis patients
Denny Ardhianto, Suharjono, Soedarsono, Umi Fatmawati
Page range: 421-427

Shallot skin profiling, computational evaluation of physicochemical properties, ADMET, and molecular docking of its components against P2Y12 receptor
Juni Ekowati, Kholidah Febriani, Itsna N. A. Yaqin, Adinda A. Wulandari, Indra H. Mulya, Kholis A. Nofianti, Achmad Syahrani
Page range: 429-437
Analysis of HMGB-1 level before and after providing atorvastatin standard therapy in coronary artery disease patients with type-2 diabetes mellitus compared to without type-2 diabetes mellitus
Widya Handayani, Suharjono, Mohammad Yogiarto
Page range: 439-446

Analysis of matrix metalloproteinase–9 levels among acute heart failure patients with ACE inhibitor therapy (Dr. Soetomo Regional General Hospital, Surabaya)
Ira Purbosari, Bambang Zubakti Zulkarnain, Muh Aminuddin, Umi Fatmawati
Page range: 447-451

The correlation between self-related adherence, asthma-related quality of life and control of asthma in adult patients
Elida Zairina, Gesmita Nugraheni, Gusti Noorrizka Veronika Achmad, Arie Sulistyarini, Yunita Nita, Arief Bakhtiar, Muhammad Amin
Page range: 453-458

Providing counseling through home pharmacy care (HPC) for hemodialysis patients with hypertension in lowering blood pressure
Rahmiyati Daud, Bambang Subakti Zulkarnain, Ivan Virnanda Amu
Page range: 459-465

Community knowledge and attitude in recognizing asthma symptoms and using medication for asthma attacks: a cross-sectional study
Arina Dery Puspitasari, Bindaria Mutmaina Prabawati, Alfian Nur Rosyid
Page range: 467-472

A study of anticoagulant therapy in patients with coronary artery disease
Arina D. Puspitasari, Daniel Dwi Christiananta Salean, Didik Hasmono, Rudy Hartono, Meity Ardiana
Page range: 473-478

The association of FKBP5 polymorphism with asthma susceptibility in asthmatic patients
Sura F. Alsaaffar, Haider A. Rasheed, Jabbar H. Yenzeel, Haider F. Ghazi
Page range: 479-484

Gastroprotective effect of fluvoxamine and ondansetron on stress–induced gastric ulcers in mice
Mahardian Rahmadi, Nily Su’a’ida, Pratiwi Yustisari, Wahyu Agung Dewandika, Elma Oktavia Hanaratri, Mareta Rindang Andarsari, Sumarno, Toetik Aryani
Page range: 485-490
**Osteoblast iron genes: real time PCR and microarray hybridization approach under hypoxia**

Prihartini Widiyanti, Hartmut Kuehn, Soetjipto Soetjipto

Page range: 491-496

**Attenuation of hyperplasia in lung parenchymal and colonic epithelial cells in DMBA–induced cancer by administering Andrographis paniculata Nees extract using animal model**

Aniek Setiya Budisatin, Ilham Bagus Sagitaras, Ika Putri Nurhayati, Nismatun Khairah, Khoirotin Nisak, Imam Susilo, Junaidi Khotib

Page range: 497-504

**N-nitrosodiethylamine induces inflammation of liver in mice**

Devy Maulidya Cahyani, Andang Miatmoko, Berlian Sarasitha Hariawan, Kusuma Eko Purwantari, Retno Sari

Page range: 505-510

**AST/ALT levels, MDA, and liver histopathology of Echinometra mathaei ethanol extract on paracetamol-induced hepatotoxicity in rats**

Angelica Kresnamurti, Dita Nurlita Rakhma, Amitasari Damayanti, Septiyan Dwi Santoso, Enggar Restryarto, Wifqi Hadinata, Iwan Sahrial Hamid

Page range: 511-516

**Development, characterization, molecular docking, and in vivo skin penetration of coenzyme Q10 nanostructured lipid carriers using tristearin and stearyl alcohol for dermal delivery**

Ni Luh Dewi Aryani, Siswandono Siswodiharjo, Widji Soeratri, Nadia Fitria Indah Sari

Page range: 517-525

**The effect of Camellia sinensis (green tea) with its active compound EGCG on neuronal cell necroptosis in Rattus norvegicus middle cerebral artery occlusion (MCAO) model**

Abdulloh Machin, Ramidha Syaharani, Imam Susilo, Muhammad Hamdan, Dyah Fauziah, Djoko Agus Purwanto

Page range: 527-531

**Hepatoprotective effect of ethanolic extract of sugarcane (Saccharum officinarum Linn.) leaves**

Ika P. Dewi, Rifdah B. Kwintana, Jihan U. Ulinnuha, Fadhillah Rachman, Fransiska M. Christiany, Diana Holidah

Page range: 533-540
Correlation between the exposure time to mobile devices and the prevalence of evaporative dry eyes as one of the symptoms of computer vision syndrome among Senior High School students in East Java, Indonesia
Rozalina Loebis, Bambang Subakti Zulkarnain, Nadhifa Zahra
Page range: 541–545

The effect of various high-fat diet on liver histology in the development of NAFLD models in mice
Mahardian Rahmadi, Ahmad Dzulfikri Nurhan, Eka Dewi Pratiwi, Devita Ardina Frameswari, Sisca Melani Panggono, Khoirrotin Nisak, Junaidi Khotib
Page range: 547–553

Fabrication and characterization of bovine hydroxyapatite-gelatin-alendronate scaffold cross-linked by glutaraldehyde for bone regeneration
Samirah, Aniek Setiya Budiatin, Ferdiansyah Mahyudin, Junaidi Khotib
Page range: 555–560

Health related quality of life among postmenopausal woman with hormone responsive HER2− breast cancer in Indonesia
Ria Etikasari, Tri Murti Andayani, Dwi Endarti, Kartika Widayati Taroeno-Hariadi
Page range: 561–565

Gender differences in the blood glucose type 2 diabetes patients with combination rapid and long acting insulin therapy
Dinda M. N. Ratri, Arina D. Puspitasari, Cahyo W. Nugroho, Budi Suprapti, Suharjono, Christoper P. Alderman
Page range: 567–570

Correlation of dietary iron intake and serum iron with thyroid stimulating hormone (TSH) and free thyroxine (FT4) levels in adult hyperthyroid patients
Utami Harjantini, Yulia Lanti Retno Dewi, Diah Hanim, Ida Nurwati
Page range: 571–576

The effect of pillbox use and education by pharmacist toward medication adherence in diabetes mellitus patients in a Primary Health Care Center in Mataram
Mahacita Andanalusia, Yunita Nita, Umi Athiyah
Page range: 577–582

Variation concentration effect of propyleneglycol, glycerin, and polyethyleneglycol 400 to physical properties and dissolution rate of loratadine liquisolid tablet
Mikhania Christiningtyas Eryani, Esti Hendradi, Siswando
Page range: 583–587
Role of *Centella asiatica* and ceramide in skin barrier improvement: a double blind clinical trial of Indonesian batik workers
Sylvia Anggraeni, Menul Ayu Umborowati, Damayanti Damayanti, Anang Endaryanto, Cita Rosita Sigit Prakoeswa
Page range: 589–593

Secondary metabolite and antipyretic effects of *Maja* (*Crescentia cujete* L.) in fever-induced mice
Teodhora, Munawarohthus Sholikha, Asniatul Ania, Ika Maruya Kusuma
Page range: 595–601

Hydration effect on kidney function and serum electrolyte in children with tumor lysis syndrome (TLS) and risk of TLS
Yulistiani, Claudia Tiffany, I. Dewa Gede Ugrasena, Mariyatul Qibtiyah
Page range: 603–609

Drug utilization study and cost analysis of adult β-thalassemia major patient therapy at Dr. Soetomo General Hospital Surabaya
Hasna Qatrunnada, Suharjono, Siprianus Ugroseno Yudho Bintoro, Siti Wahyuni
Page range: 611–616

The role of hyperbaric oxygen to platelet aggregation in noninsulin-dependent diabetes mellitus (NIDDM)
Prihartini Widiyanti, Purnomo Suryohudoyo
Page range: 617–621

Cocrystal formation of loratadine-succinic acid and its improved solubility
Dwi Setyawan, Firdaus Rendra Adyaksa, Hanny Lystia Sari, Diajeng Putri Paramita, Retno Sari
Page range: 623–630

The role of chondroitin sulfate to bone healing indicators and compressive strength
Herry Wibowo, Prihartini Widiyanti, Syaifullah Asmiragani
Page range: 631–635

The effects of quercetin on the expression of SREBP-1c mRNA in high-fat diet-induced NAFLD in mice
Jamal Nasser Saleh Al-maamari, Mahardian Rahmadi, Sisca Melani Panggono, Devita Ardina Prameswari, Eka Dewi Pratiwi, Chrismawan Ardianto, Santhra Segaran Balan, Budi Suprapti
Analysis of stress ulcer prophylaxis drug regimens in surgical patients
Dhani Wijaya, Subarjono, Fendy Matulatan, Elfri Padolo
Page range: 645–649

The stability and irritability study of the chitosan–Aloe vera spray gel as wound healing
Dini Retnowati, Retno Sari, Esti Hendradi, Septiani Septiani
Page range: 651–656

Effectiveness of citicoline in pediatric patients with refractive amblyopia in Surabaya, East Java, Indonesia
Rozalina Loebis, Bambang Subakti Zulkarnain, Fitri Amalia Siswanto
Page range: 657–661

The thermodynamic study of p-methoxycinnamic acid inclusion complex formation, using β-cyclodextrin and hydroxypropyl-β-cyclodextrin
Dewi Isadiartuti, Noorma Rosita, Juni Ekowati, Achmad Syahrani, Toetik Ariyani, M. Ainur Rifqi
Page range: 663–667

The effect of chitosan type and drug-chitosan ratio on physical characteristics and release profile of ketoprofen microparticles prepared by spray drying
Muhammad A. S. Rijal, Hanah Masitah, Fanny Purvitasari, Retno Sari
Page range: 669–673

The maximum dose and duration in the therapy single use methotrexate to achieve remission by rheumatoid arthritis patients through disease activity score 28 (DAS28)
Anisyah Achmad, Tika Yasmin Rahmayanti, Bagus Putu Putra Suryana
Page range: 675–680

Knowledge, attitudes, and practices (KAP) towards COVID-19 among university students in Pakistan: a cross-sectional study
Shah Faisal, Junaidi Khotib, Elida Zairina
Page range: 681–686
The impact of glutaraldehyde on the characteristics of bovine hydroxyapatite-gelatin based bone scaffold as gentamicin delivery system
Aniek Setiya Budiatin, Maria Apriliani Gani, Chrismawan Ardianto, Samirah, Sahrati Yudiaprijah Daeng Pattah, Fitroh Mubarokah, Junaidi Khotib
Page range: 687–691

Analysis of the use of antibiotics profile and factors of surgical site infections study on digestive and oncology surgeries
Lisa Narulita, Suharjono, Kuntaman, Mohammad Akram
Page range: 693–700

Second internal transcribed spacer (ITS-2) as genetic marker for molecular characterization of Sarcoptes scabiei in rabbits from several areas of East Java, Indonesia
Nunuk Dyah Retno Lastuti, Nur Rusdiana, Poedji Hastutiek
Page range: 701–705

Design of gossypetin derivatives based on naturally occurring flavonoid in Hibiscus sabdaria and the molecular docking as antibacterial agents
Nuzul W. Diyah, Isnaeni, Shabrina W. Hidayati, Bambang T. Purwanto, Siswandono
Page range: 707–714

Discovery of new targeting agents against GAPDH receptor for antituberculosis drug delivery
Muhammad Amirul Asyraf Noh, Siti Sarah Fazalul Rahiman, Habibah A Wahab, Amirah Mohd Gazzali
Page range: 715–722

The effect of red passion fruit (Passiflora edulis Sims.) fermentation time on its activity against Extended Strain Methicillin-Resistant (ESBL) Escherichia coli and Methicillin-Resistant Staphylococcus aureus (MRSA)
Iif Hanifa Nurrosyidah, Ni Made Mertaniasih, Isnaeni
Page range: 723–727

Antibiotic use on acute respiratory tract infection nonpneumonia and nonspecific diarrhea in Primary Health Care Centre in Banjarbaru City, South Kalimantan, Indonesia
Rizky Liestya Wardani, Suharjono, Kuntaman, Agus Widjaja
Page range: 729–735

Screening of anti-HIV activities in ethanol extract and fractions from Ficus fistulosa leaves
Siti Qamariyah Khairunisa, Dwi Wahyu Indriati, Lidya Tumewu, Aty Widyawaruyanti, Nasronudin Nasronudin
Page range: 737–742
The characteristics of lactic acid bacteria isolated from fermented food as potential probiotics
Victoria Yulita Fitriani, Budi Suprapti, Muhammad Amin
Page range: 743–749

Profile of gyrA gene mutation in clinical isolate of levofloxacin resistant Escherichia coli
Alifia Risma Fahmi, Suharjono, Kuntaman
Page range: 751–754

Antimicrobial activity of Centella asiatica and Gigantochloa apus
Siti Mudaliana
Page range: 755–759

Drug-related problems of antibiotic use in gastroenteritis related to patient therapy outcomes at Universitas Gadjah Mada Hospital
Fivy Kurniawati, Nanang Munif Yasin, Farida Aulia, Gidfrue Vinanda Krisha
Page range: 761–766

The impact of suitability of empirical antibiotics use on therapeutic outcome of respiratory tract infection patients at inpatient wards of Universitas Gadjah Mada Academic Hospital
Fivy Kurniawati, Nanang Munif Yasin, Safina Nur Azizah, Silvia Ayu Purbaningtyas
Page range: 767–771

Genetic profile mutation rpoB in clinical isolate of rifampicin-resistant Staphylococcus aureus
Risa Zulfiana, Suharjono, Kuntaman
Page range: 773–776

Hematological side effect analysis of linezolid in MDR-TB patients with individual therapy
Novan Yusuf Indra Pratama, Bambang Subakti Zulkamain, Soedarsono, Umi Fatmawati
Page range: 777–781

Adverse drug reaction and its management in tuberculosis patients with multidrug resistance: a retrospective study
Wenny Putri Nilamsari, Muhammad Fajar Rizqi, Natasya Olga Regina, Prastuti Asta Wulaningrum, Umi Fatmawati
Page range: 783–787
Analysis of prophylactic antibiotic use and risk factor of postoperative infection in urological surgery patients
Ratri Rokhani, Suharjono, Kuntaman, Mohammad Akram
Page range: 789–794

Molecular docking studies of Nigella sativa L and Curcuma xanthorrhiza Roxb secondary metabolites against histamine N-methyltransferase with their ADMET prediction
Ahmad Dzulfikri Nurhan, Maria Apriliani Gani, Aniek Setiya Budiatin, Siswando Siswodihardjo, Junaidi Khotib
Page range: 795–802

Prediction of compounds with antiosteoporosis activity in Chrysophyllum cainito L. leaves through in silico approach
Burhan Ma’arif, Hilwa Fitri, Nisfatul Lailatus Saidah, Luqman Alfani Najib, Achmad Hamdan Yuwafi, Ria Ramadhani Dwi Atmajaya, Fidia Rizkiyah Inayatillah, Melina Ratna Dianti, Hening Laswati, Mangestuti Agil
Page range: 803–808

Phyllanthin and hypophyllanthin, the isolated compounds of Phyllanthus niruri in inhibit protein receptor of corona virus (COVID-19) through in silico approach
Honey Dzikri Marhaeny, Aty Widyawaruyanti, Tri Widiandani, Achmad Fuad Hafid, Tutik Sri Wahyun
Page range: 809–815

Cratoxylum sumatranum stem bark exhibited antimalarial activity by Lactate Dehydrogenase (LDH) assay
Lidya Tumewu, Fendi Yoga Wardana, Hilkatul Ilmi, Adita Ayu Permanasari, Achmad Fuad Hafid, Aty Widyawaruyanti
Page range: 817–822

Endophytic fungi inhabiting Physalis angulata L. plant: diversity, antioxidant, and antibacterial activities of their ethyl acetate extracts
Kartika Dyah Palupi, Muhammad Ilyas, Andria Agusta
Page range: 823–829

Exploration of several plants from Baung Forest on bone formation cell models
Retno Widyowati, Neny Purwitasari, Rice Disi Oktarina, Wiwied Ekasari, Saarah Khairunnisa, Hsin–I. Chang
Page range: 831–837

In vitro antimalarial activity of Garcinia parvifolia Miq. Stem extracts and fractions on Plasmodium falciparum lactate dehydrogenase (LDH) assay
Antioxidant and antiviral potency of Begonia medicinalis fractions
Muhammad Sulaiman Zubair, Siti Qamariyah Khairunisa, Evi Sulastri, Ilhwan, Agustinus Widodo, Nasronudin, Ramadanil Pitopang
Page range: 845–851

Artocarpus sericicarpus stem bark contains antimalarial substances against Plasmodium falciparum
Lidya Tumewu, Lutfah Qurrota A'yun, Hilkatul Ilmi, Achmad Fuad Hafid, Aty Widyawaruyanti
Page range: 853–858

Formulation and characterization of Eleutherine palmifolia extract-loaded self-nanoemulsifying drug delivery system (SNEDDS)
Rahmi Annisa, Mochammad Yuwono, Esti Hendradi
Page range: 859–865

Analytical method for the determination of curcumin entrapped in polymeric micellar powder using HPLC
Helmy Yusuf, Nina Wijiani, Rizka Arifa Rahmawati, Riesta Primaharinastiti, M. Agus Syamsur Rijal, Dewi Isadiartuti
Page range: 867–873

Challenges in the provision of natural medicines by community pharmacists in East Java Province, Indonesia
Hanni P. Puspitasari, Dhita Fatmaningrum, Sa’adatus Zahro, Shofi Salsabila, Zulfia A. Rizqulloh, Ana Yuda, Mufarrirah, Anila I. Sukorini, Neny Purwitasari
Page range: 875–880

In vitro and in silico analysis of phytochemical compounds of 96% ethanol extract of semanggi (Marsilea crenata Presl.) leaves as a bone formation agent
Agnis P.R. Aditama, Burhan Ma’arif, Hening Laswati, Mangestuti Agil
Page range: 881–887

Inhibitory activity of Urena lobata leaf extract on alpha-amylase and alpha-glucosidase: in vitro and in silico approach
Yudi Purnomo, Juliah Makdasari, Faiqoh Inayah Fatahillah
Page range: 889–894
Case Report

Effect of hydrocortisone on hypocorticolism caused by pituitary adenoma
Niswah N. Qonita, Hanik B. Hidayati
Page range: 895-898
Shallot skin profiling, computational evaluation of physicochemical properties, ADMET, and molecular docking of its components against P2Y12 receptor

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 cardiovascular 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-fluoroquinoxalin-4-y]amine, benzo[a] heptalene, N-(trifluoroacetyl) methyl-N-deacetyl-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 profiling; 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 thrombembolism, 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]
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 be influenced by the physicochemical properties [18]. Lipinski et al. has formulated several criteria regarding the physical and chemical properties of compounds that can demonstrate its oral bioavailability, 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 skins, 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 FeCl3, 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 FeCl3 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 pm 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 P2Y12 receptor, which can been downloaded from Protein Data Bank (http://www.rcsb.org). This P2Y12 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. The docking study was carried out 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 1. 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 ranges from 0 (Benzo[a]heptalene) until 7 (N-(trifluoroacetyl)methyl-N-deacetyl-Colchicine and Querc- etin), from 0 (Benzo[a]heptalene) until 10 (Natalensine, 3,5-dinitrobenzoate), and from 0 (Benzo[a]heptalene) until 5 (Quercetin).

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 FeCl₃. 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 ranges from 0 (Benzo[a]heptalene) until 7 (N-(trifluoroacetyl)methyl-N-deacetyl-Colchicine and Quercetin), 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 P2Y12 receptors.

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

<table>
<thead>
<tr>
<th>RT</th>
<th>Compound name</th>
<th>%Normality</th>
<th>Qual</th>
</tr>
</thead>
<tbody>
<tr>
<td>28.34</td>
<td>Natalensine, 3,5-dinitrobenzoate</td>
<td>13.43%</td>
<td>30</td>
</tr>
<tr>
<td>28.85 and Bis[2-(2-fluorophenyl)-6-fluoroquinolin-4-yl]amine</td>
<td>36.90%</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>33.05</td>
<td>6-fluoroquinolin-4-yl]amine</td>
<td>17.43%</td>
<td>95</td>
</tr>
<tr>
<td>29.13</td>
<td>Benzo[a]heptalene</td>
<td>32.23%</td>
<td>35</td>
</tr>
<tr>
<td>29.30</td>
<td>N-(trifluoroacetyl)methyl-N-deacetyl-colchicine</td>
<td>32.23%</td>
<td>35</td>
</tr>
</tbody>
</table>

### Table 2: Quercetin and polyphenol content in extract.

<table>
<thead>
<tr>
<th>Content</th>
<th>Quantity in extract</th>
<th>Mean % (b/b) ± RPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quercetin</td>
<td>4.61 ± 2.43</td>
<td></td>
</tr>
<tr>
<td>Polyphenol</td>
<td>11.14 ± 5.12</td>
<td></td>
</tr>
</tbody>
</table>

RPD: relative percent difference.
Table 3: Physicochemical and pharmacokinetic prediction.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>MW</th>
<th>Boiling point, K</th>
<th>Melting point, K</th>
<th>Log p</th>
<th>Bond rotation</th>
<th>HBA</th>
<th>HBD</th>
<th>PSA</th>
<th>Water absorption</th>
<th>Intestinal absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quercetin</td>
<td><img src="image" alt="Quercetin structure" /></td>
<td>302.238</td>
<td>1135.37</td>
<td>970.62</td>
<td>1.988</td>
<td>1</td>
<td>7</td>
<td>5</td>
<td>122.108</td>
<td>−2.925</td>
<td>77.207</td>
</tr>
<tr>
<td>Bis[2- (2-fluorophenyl)-6-fluorquinolin-4-yl] amine</td>
<td><img src="image" alt="Bis(2-fluorophenyl)-6-fluorquinolin-4-yl amine structure" /></td>
<td>495.479</td>
<td>1225.17</td>
<td>896.7</td>
<td>8.417</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>208.617</td>
<td>−3.577</td>
<td>93.87</td>
</tr>
<tr>
<td>N-(trifluoroacetyl) methyl- N-deacetyl-colchicine</td>
<td><img src="image" alt="N-(trifluoroacetyl) methyl-N-deacetyl-colchicine structure" /></td>
<td>467.44</td>
<td>1076.21</td>
<td>754.77</td>
<td>3.4565</td>
<td>7</td>
<td>7</td>
<td>1</td>
<td>187.966</td>
<td>−3.781</td>
<td>93.15</td>
</tr>
<tr>
<td>Benzo[a]heptalene</td>
<td><img src="image" alt="Benzo[a]heptalene structure" /></td>
<td>204.272</td>
<td>643</td>
<td>367.64</td>
<td>2.24</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>94.932</td>
<td>−3.691</td>
<td>99.286</td>
</tr>
<tr>
<td>Natalensine, 3,5-dinitrobenzoate</td>
<td><img src="image" alt="Natalensine, 3,5-dinitrobenzoate structure" /></td>
<td>495.444</td>
<td>–</td>
<td>–</td>
<td>2.8678</td>
<td>5</td>
<td>10</td>
<td>0</td>
<td>203.836</td>
<td>−4.896</td>
<td>94.254</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>Absorption</th>
<th>Distribution</th>
<th>Metabolism</th>
<th>Excretion</th>
<th>Toxicity</th>
<th>LD50</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Skin permeability</td>
<td>Caco-2 permeability</td>
<td>VDss (human)</td>
<td>BBB permeability</td>
<td>CNS permeability</td>
<td>CYP2D6 substrate</td>
</tr>
<tr>
<td>Quercetin</td>
<td>−2.735</td>
<td>−0.229</td>
<td>1.559</td>
<td>−1.098</td>
<td>−3.065</td>
<td>No</td>
</tr>
<tr>
<td>Bis[2- (2-fluorophenyl)-6-fluorquinolin-4-yl] amine</td>
<td>−2.735</td>
<td>1.165</td>
<td>−0.826</td>
<td>0.343</td>
<td>−0.819</td>
<td>No</td>
</tr>
<tr>
<td>N-(trifluoroacetyl) methyl- N-deacetyl-colchicine</td>
<td>−2.716</td>
<td>1.139</td>
<td>0.833</td>
<td>−1.231</td>
<td>−3.21</td>
<td>No</td>
</tr>
<tr>
<td>Benzo[a]heptalene</td>
<td>−1.645</td>
<td>1.539</td>
<td>0.207</td>
<td>0.619</td>
<td>−1.986</td>
<td>No</td>
</tr>
<tr>
<td>Natalensine, 3,5-dinitrobenzoate</td>
<td>−2.737</td>
<td>−0.006</td>
<td>0.235</td>
<td>−0.891</td>
<td>−2.55</td>
<td>No</td>
</tr>
</tbody>
</table>
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)methyltrihydrogen diphosphate against P2Y12 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)methyltrihydrogen 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
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 molecule, which used as antithrombolysis. ADP-induced platelet aggregation test shows that the stronger antithrombolytic activity is attributable to its moiety [32, 33]. Therefore, further research on polyphenols as antithrombolytic is necessary. In this research, extraction of shallot skin, which carried out ultrasonic, had the amount of polyphenols of 11.14%. Litertures 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 antithrombolyics. ADP-induced platelet aggregation test shows that the stronger antithrombolytic activity is attributable to its moiety [32, 33]. Therefore, further research on polyphenols as antithrombolytic 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 hydroxy 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.

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

<table>
<thead>
<tr>
<th>Compound name</th>
<th>MDS</th>
<th>Amino acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quercetin</td>
<td></td>
<td>−128.010 Arg 256, Asn 159, Asn 191, Cys 194, His 187 Met 152, Ser 156, Tyr 105</td>
</tr>
<tr>
<td>Bis[2-(2-fluorophenyl)-6-fluoroquinolin-4-yl]amine</td>
<td></td>
<td>−116.863 Asn 159, Asn 191, Cys 97, Cys 194, Lys 179, Met 152, Phe 106, Ser 101, Ser 156, Tyr 109</td>
</tr>
<tr>
<td>N-(trifluoroacetyl)methyl-N-deacetyl-colchicine</td>
<td></td>
<td>−157.041 Arg 93, Cys 97, Cys 175, Gln 263, Lys 80, Lys 179, Lys 280, Ser 101, Tyr 105, Tyr 259</td>
</tr>
<tr>
<td>Benzo[a]heptalene</td>
<td>−122.252 Arg 93, Cys 175, Gln 263, Lys 80, Lys 280, Ser 101, Tyr 105, Tyr 259, Val 96, Val 102</td>
<td></td>
</tr>
<tr>
<td>Natalensine, 3,5-dinitrobenzoate</td>
<td></td>
<td>−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</td>
</tr>
</tbody>
</table>

One example of phenolic compound is ferulic acid, which used as antithrombolyics. ADP-induced platelet aggregation test shows that the stronger antithrombolytic activity is attributable to its moiety [32, 33]. Therefore, further research on polyphenols as antithrombolytic 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.

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(phospholipase C, cAMP phosphodiesterase, cyclooxygenase, 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-deacetyl-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 × 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-deacetyl-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 3.355.

Prediction of antiplatelet activity was carried out at the P2Y12 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 clopidogrel, which is highly metabolized by the CYP450 enzyme [47].

Based on the in silico test against the P2Y12 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 phosphate 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, so that its binding ability is smaller, it still does not eliminate the possibility that quercetin can be used against the P2Y12 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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Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Not applicable.

Ethical approval: Not applicable.

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Cites per document

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Documents during the three previous years.

External citations are calculated by subtracting the number of self-citations from the total number of citations received by the journal's documents.

International Collaboration accounts for the articles that have been produced by researchers from several countries. The chart shows the ratio of a journal's documents signed by researchers from more than one country; that is including more than one country address.

Citable documents

Non-citable documents

Not every article in a journal is considered primary research and therefore "citable", this chart shows the ratio of a journal's articles including substantial research (research articles, conference papers and reviews) in three year windows vs. those documents other than research articles, reviews and conference papers.

Cited documents

Uncited documents

Ratio of a journal's items, grouped in three years windows, that have been cited at least once vs. those not cited during the following year.

Oman 11 months ago

How much money to publish in this journal

reply

Melanie Ortiz 11 months ago

SCImago Team
Dear Oman,

thank you for contacting us.
Unfortunately, we cannot help you with your request, we suggest you visit the journal's homepage or contact the journal's editorial staff, so they could inform you more deeply.

Best Regards, SCImago Team

Daniel Orieke 12 months ago

Please how do you get original article submitted.

reply

Melanie Ortiz 12 months ago

Dear Daniel, thank you very much for your comment, we suggest you look for author's instructions/submission guidelines in the journal's website. Best Regards, SCImago Team

dr jhanvi vaghela 2 years ago

Is Journal of Basic and Clinical Physiology and Pharmacology is online only journal??

reply

Melanie Ortiz 2 years ago

Dear Jhanvi,

thank you for contacting us.

Sorry to tell you that SCImago Journal & Country Rank is not a journal. SJR is a portal with scientometric indicators of journals indexed in Elsevier/Scopus.

Unfortunately, we cannot help you with your request, we suggest you to visit the journal's homepage or contact the journal's editorial staff, so they could inform you more deeply.

Best Regards, SCImago Team

Nilufar 2 years ago

Dear Sir/Madam,

I couldn't find how to publish the article at this journal. Could you possibly send the requirements of publishing at this journal, please?

Kindest regards,
Nilufar

reply
Dear Nilufar,

You can see the updated information just above. Best Regards, SCImago Team

The users of Scimago Journal & Country Rank have the possibility to dialogue through comments linked to a specific journal. The purpose is to have a forum in which general doubts about the processes of publication in the journal, experiences and other issues derived from the publication of papers are resolved. For topics on particular articles, maintain the dialogue through the usual channels with your editor.

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