LFER and 3D-QSAR Analysis of Febrifugine Derivatives against *Plasmodium falciparum* FCR-3 Strain

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ABSTRACT
Malaria is a serious disease caused by Plasmodium through the bite of the female Anopheles mosquito. Due to resistance to artemisin, a first-line antimalarial, new compounds are needed. This study aims to obtain a QSAR model from febrifugine derivatives against the *Plasmodium falciparum* FCR-3 strain. 3D-QSAR modelling using Cloud-3D QSAR, and LFER (Linear Free Energy Relationship) Hansch QSAR equation using DTC QSAR have been carried out in this study. The results showed that the best 3D-QSAR model indicating the addition of steric substituents on C6 and C7 of quinazolinone, C4 and C5 of piperidine, and electronic substituents on C5 might increase activity. Furthermore, the best LFER Hansch QSAR equation is shown by pIC50 = 0,069(±0,0009) $(logP)^2$ +3,5234(±0,0461) (n = 40 R^2 = 0.9938; Q^2 LOO = 0.9926; R_m^2 average = 0.9895; R^2-Q^2 LOO = 0.0012; ΔR_m^2 = 0.0037; Q^2 F1 = 0.9956; Q^2 F2 = 0.9955; CCC = 0.9978). Based on the LFER Hansch QSAR equation, the physicochemical parameter which must be considered to increase the activity is the lipophilic parameter. In addition, febrifugine and its derivatives are predicted to possess a good ADMET profile. The results of this QSAR model can be used to develop further antimalarials.

Keywords: QSAR*, Febrifugine, Antimalaria, FCR-3 strain*

1. INTRODUCTION

Malaria is one of the deadliest diseases caused by *Plasmodium falciparum* infection transmitted via the Anopheles female mosquito [1]. WHO has recommended Artemisinin-Based Combination Therapy as the first-line therapy in malaria treatment [2]. However, several cases of parasite resistance [3] point out the necessity for improvement in dealing with malaria, one of which is *via* drug discovery.

Febrifugine is a quinazolinone-type alkaloid isolated from Dichroa febrifuga [4], which has long been known as an antimalarial agent in Traditional Chinese Medicine [5,6]. However, it also possesses significant side effects, such as nausea, vomiting, and hepatotoxicity. Febrifugine inhibits *Plasmodium falciparum* prolyl-tRNA synthetase, which has been proven an antimalarial target [7]. It inhibits this enzyme by occupying active pockets of proline and the 3' end of tRNA [7,8].

Various derivates of febrifugine have been synthesized and have their potencies evaluated to obtain the most potent analog with low to minimal side effects [9-13]. This study created a QSAR model using the three-dimensional and LFER Hansch approach. The outcome is to obtain the most suitable correlation model, which can guide the design of novel febrifugin analogs with significant improvement in antimalarial activity. In addition, the ADMET profile of febrifugin and its derivatives have been characterized *in silico* to understand their pharmacokinetics characteristic better.

2. MATERIALS & METHODS

2.1. Dataset Preparation

This study focused on the QSAR model between febrifugine derivatives and their activity against the FCR-3 cell line. A literature study shows sixty molecules have been tested against this cell line, 10 of which do not yield specific IC50 value [9-13]. Therefore, 50 compounds will

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be used in QSAR modeling. These compounds were built in 1D and 2D, and their activity value was converted to pIC50. On the other hand, ADMET prediction was performed using the full data set.

2.2. LFER Hansch QSAR Model

LFER Hansch equation was built using DTC-QSAR software (available from https://dtclab.webs.com/software-tools). Three types of descriptors were generated in this study (lipophilic, steric, electronic) as independent variables. LogP and $(LogP)^2$ as lipophilic descriptors were calculated using the pkCSM web server [14]. Molecular weight and solvent-accessible surface area (SASA) as steric descriptors were calculated using MarvinSketch 22.5 (available from https://chemaxon.com). EHOMO, ELUMO, and ETOT as electronic descriptors were calculated using MOPAC2016 [15] (available from https://openmopac.net/MOPAC2016.html), where 3D structures were generated using PM6 basis set [16]. Before the QSAR model building, the dataset was split into a training set and a test set with a ratio of 4:1 using the Kennard-Stones algorithm [17]. Various statistical parameter was used to evaluate the quality and validity of the QSAR model, such as $R^2 > 0{,}7$; Q^2 LOO > 0,6; R^2-Q^2 LOO < 0,1; $\underline{R_m^2} > 0{,}65$; $\Delta R_m^2 < 0{,}2$; Q^2F1, $Q^2F2 > 0{,}7$; and CCC > 0,85 [18].

2.3. 3D QSAR Model

A three-dimensional QSAR model was built using the webserver Cloud-3D QSAR [19]. Compounds in the dataset were prepared in a 1D format to be submitted to the web server. Similar to the Hansch model, a dataset was split similarly to validate the result. The 3D QSAR model is visualized as a contour map with specific colors indicating the most prominent effect in the particular region. Steric group addition is guided by green and yellow, where the former indicates a positive effect on activity, while the latter indicates otherwise. Electronic effects are denoted with red and blue, where the former indicates the desirable addition of the negatively charged group, while the latter indicates the desirable addition of the positively charged group [19,20].

2.4. ADMET Prediction

ADME parameters of 60 febrifugine derivatives were predicted using the pkCSM web server [14]. These parameters were human intestinal absorption (HIA), the volume of distribution at steady state condition (VDSS), various cytochrome-P450 related interactions, and total clearance value. In addition, toxicity prediction was performed using ProTox-II [21]. This web server yields predicted toxicity value in LD50, which is then classified into six classes of oral toxicity.

3. RESULTS & DISCUSSION

Quantitative Structure-Activity Relationships (QSAR) is one of the approaches which can be implemented to explore the correlation between chemical structures and their bioactivity [22]. LFER Hansch is among the earliest method, founded by the postulate that the bioactivity of a compound is influenced by lipophilic, steric, and electronic aspects [23]. This method created a mathematical model between various febrifugine analogs and their antimalarial activity. The result showed that the second order of LogP plays an important role in defining the structure-activity correlation. According to McFarland's hypothesis, nonlinear interaction between LogP and activity is likely to be observed since a molecule must pass the phospholipid bilayer membrane before interacting with the target receptor [24]. However, this current model is limited in its applicability domain from the dataset of febrifugine analogs with a pIC50 value of more than 5.

$$pIC50 = 0{,}069(\pm 0{,}0009)\,(logP)^2 + 3{,}5234(\pm 0{,}0461) \quad (1)$$

($n = 40$ $R^2 = 0.9938$ Q^2 LOO $= 0.9926$ R_m^2 average $= 0.9895$ R^2-Q^2 LOO $= 0.0012$ $\Delta R_m^2 = 0.0037$ Q^2 F1 $= 0.9956$ Q^2 F2 $= 0.9955$ CCC $= 0.9978$)

3D-QSAR is a QSAR model that correlates various molecules' three-dimensional structures with their biological activity. This method uses an atom-based descriptor derived from the spatial representation of molecules [20]. Here, the 3D QSAR model was formulated using web server Cloud-3D QSAR, which uses the CoMFA approach and partial-least square for statistical evaluation. The resulting model should correspond with statistical parameters such as R^2, Q^2, and R^2_{pred} [25]. Our best model complies with the parameters ($R^2 = 0.9393$ $Q^2 = 0.6098$) but with a poor R^2_{pred} value ($R^2_{pred} = -1.3418$) which indicated low predictability. The contour map showed that steric functional group addition is necessary for C6 and 7 of quinazolinone and C4 and 5 of piperidine. Meanwhile, further improvement could be expected by adding a negatively charged functional group in C5 of quinazolinone.

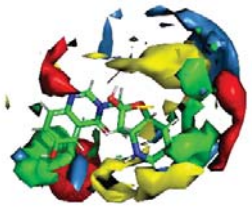


Figure 1 3D QSAR contour map of febrifugine and their analogs

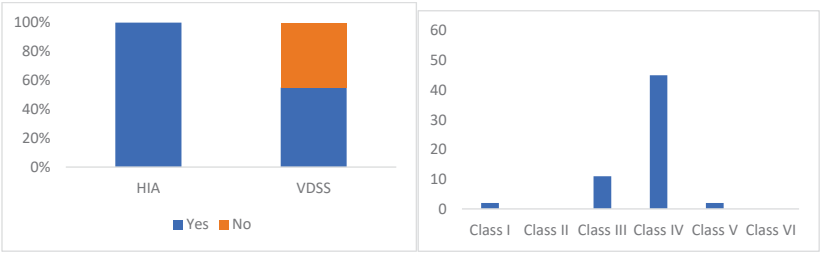
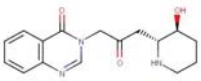
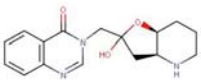
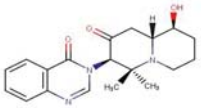
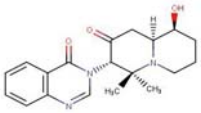
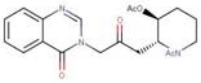
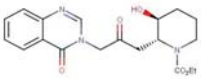
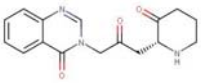
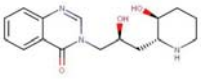
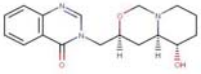
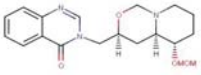
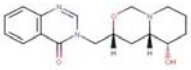
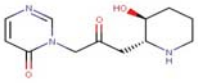
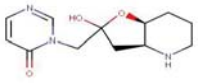
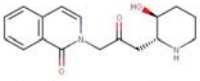
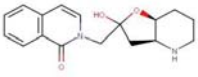
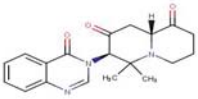
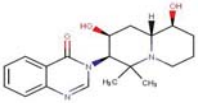
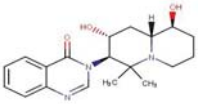
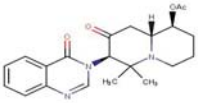
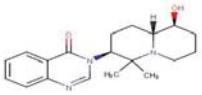
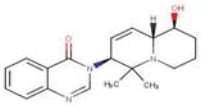
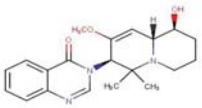
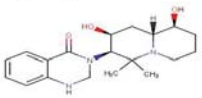
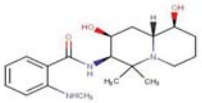
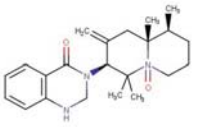
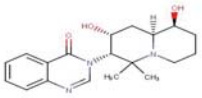
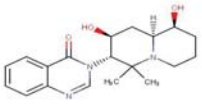
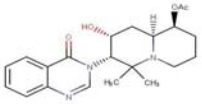
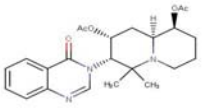
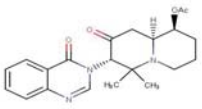


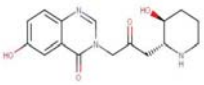
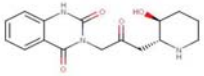
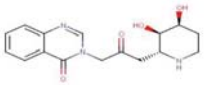
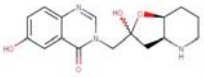
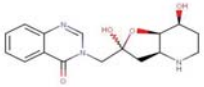
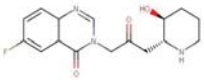
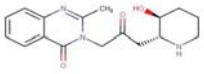
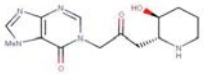
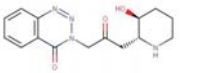
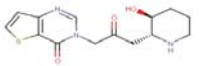
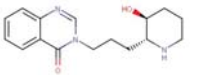
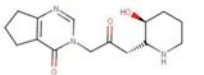
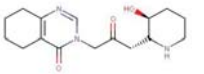
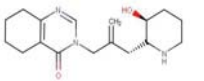
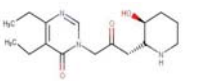
Figure 2 Prediction of absorption, distribution (left), and oral toxicity class (right) of 60 febrifugine analogs

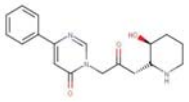
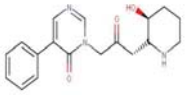
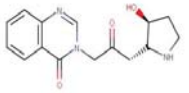
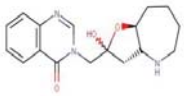
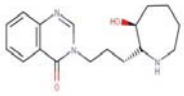
Table 1. Febrifugine analogs dataset used in QSAR model building

Reference	Compound	IC50 (μM)
[9]		7.0×10^{-4}
[9]		3.4×10^{-3}
[9]		1.6×10^{-3}
[9]		2.8×10^{-3}
[10]		9.1×10^{-1}
[10]		4.8
[10]		2.0×10^{-2}
[10]		2.0×10^{-2}
[10]		3.7×10^{-3}
[10]		8.6×10^{-3}

Reference	Compound	IC50 (μM)
[10]		8.4×10^{-1}
[10]		6.0×10^{-1}
[10]		4.0×10^{-2}
[10]		5.0×10^{-1}
[10]		2.1
[10]		1.9×10^{-3}
[10]		4.0×10^{-1}
[10]		3.0×10^{-1}
[10]		3.6×10^{-3}

Reference	Compound	IC50 (μM)
[10]		8.3×10^{-1}
[10]		4.8
[10]		1.3
[10]		4.2×10^{-1}
[10]		6.0×10^{-1}
[10]		1.0×10^{-1}
[10]		8.0×10^{-1}
[10]		3.4
[11]		4.0×10^{-1}
[11]		7.0
[11]		1.9×10^{-2}

Reference	Compound	IC50 (μM)
[12]		2.2×10^{-3}
[12]		6.6
[12]		2.2×10^{-2}
[12]		2.7×10^{-4}
[12]		1.5×10^{-1}
[13]		2.3×10^{-3}
[13]		0.36
[13]		1.66
[13]		0.51
[13]		9.95×10^{-3}
[13]		0.0783
[14]		0.256
[14]		0.258
[14]		0.128
[14]		0.640

Reference	Compound	IC50 (μM)
[14]		0.286
[14]		0.128
[14]		2.126
[14]		0.390
[14]		1.808

In silico predictions were performed to assess the profile of ADMET parameters of febrifugine analogs. Generally, all febrifugine analogs possess acceptable absorption and distribution, which is indicated by an HIA value of more than 30% [26] and a VDSS value of more than 0.45 [27], respectively. Cytochrome P450 interaction prediction yielded 11 compounds as 3A4 substrates, 8 as 1A2 inhibitors, and one as 2C19 inhibitors. The average value of log total clearance from 60 compounds is 0.971 (ml/min/kg). This value represents the rate of hepatic and renal excretion of a compound, where a high value indicates a faster excretion process. Ultimately, LD50 analysis of febrifugin analogs showed that most of the compound is classified in GHS Class IV for acute oral toxicity [26].

4. CONCLUSION

We have developed LFER Hansch and 3D-QSAR models for febrifugine derivates against *P. falciparum* strain FCR-3. It is argued that $(LogP)^2$ is important in improving antimalarial activity. In addition, substituting the steric functional group in the quinazolinone and piperidine ring of febrifugine could improve their bioactivity. However, further dataset and method selection are still needed to validate the 3D-QSAR model.

AUTHORS' CONTRIBUTIONS

Tegar Achsendo Yuniarta and Dini Kesuma conceptualized the study, Nur Aina performed data collection, Nur Aina and Tegar Achsendo Yuniarta performed data analysis, Nur Aina and Tegar Achsendo Yuniarta wrote the manuscript, all authors have read and agreed with the manuscript.

ACKNOWLEDGMENTS

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All of the articles in this proceedings volume have been presented at the 4th International Conference on Natural Resources and Life Sciences

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Systematic Literature Review: Side Effect of *Moringa oleifera* Lam.

Deborah Felinda Hari Wijaya, Alfian Hendra Krisnawan, Oeke Yunita, Krisyanti Budipramana, Karina Citra Rani, Nikmatul Ikhrom Eka Jayani

Moringa oleifera Lam. (Drumstick tree) is a herbal plant commonly found in subtropical and tropical areas such as Indonesia. Moringa plants have been widely used because they have many pharmacological effects. In addition, due to the high consumption of Moringa, there still needs to be monitoring regarding...

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The administration of prophylactic antibiotics in hernia surgery patients is currently controversial, with varying opinions regarding their necessity. The European Hernia Society guideline does not recommend prophylactic antibiotics in patients with hernia surgery, while recent studies found that prophylactic...

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Analysis of Factors Affecting Adherence to Anti-Retroviral Treatment among HIV/AIDS Out-patients at the Dinoyo Public Health Centre

Annisa Lazuardy, Yosi Irawati Wibowo, Adji Prayitno Setiadi

There is an increasing prevalence of HIV/AIDS cases in Indonesia, particularly in Malang City, a tourist and educational destination. This study aimed to identify the characteristics of people living with HIV/AIDS (PLWHA) as well as to analyze their adherence to anti-retroviral (ARV) treatment and the...

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Fadilla Sherlyna, Muhammad Ilham Fahri, Arief Koeswanto, Dandan Wang

Cardiovascular Diseases (CVDs) are a growing global concern, including in Indonesia. By 2021, strokes were the leading cause of cardiovascular diseases (CVD), affecting 87% of the global population, while in 2018, 33.3% of Indonesians experienced CVD primarily due to strokes. Thrombolysis mediated by...

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Merry Meryam Martgrita, Nehemia Roito Hutajulu, Hanna Gretty Manik, Adelina Manurung

Food industry waste, especially fruit peels, increases every year and their disposal can cause environmental pollution that can affect health. Fruit peels are known to contain antioxidant and antibacterial compounds, and their utilization can provide more value to fruit peel waste. This literature review...

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Estimation of Shelf-life of Porang Glucomannan Analog Rice By Accelerated Shelf-life Testing (ASLT) Method

Michael Surya Dharma, Yayon Pamula Mukti, Gisela Buschle-Diller, Ardhia Deasy Rosita Dewi

Analog rice is rice made from some or all non-rice ingredients and was created as a food diversification product so that it can be an alternative staple food to replace rice produced from rice. The shelf-life of food products can be determined using the ASLT method, which in principle accelerates the...

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Fortification of Dayak Onion Extract (*Eleutherine palmifolia* (L.) Merr.) to Jelly Drink as a Functional Food

Yayon Pamula Mukti, Berliana Yusup, Ardhia Deasy Rosita Dewi, Se Chan Kang

Indonesia is a nation characterized by a diverse array of plant species that possess notable health benefits. Among these botanical resources is the Dayak onion, scientifically known as Eleutherine palmifolia (L.) Merr. The Dayak Tribe – an indigenous people of Borneo's island has historically utilized...

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The Effect of *Bajakah Tampala* Stem (*Spatholobus littoralis* Hassk) Extract on Clotting Time in Vitro

Noza N. Moyananda, Rachmad P. Armanto, Mariana Wahjudi

Wounds that are not treated immediately will have a risk for the patient; the risk is infection. The risk of this infection can be reduced by stopping the bleeding as soon as possible. One way to accelerate the bleeding to stop is by giving haemostatic agents. One source of this haemostatic agent can...

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Oeke Yunita, Erlin Theterissa

Worldwide, the use of herbal medications is still growing quickly as more customers turn to these treatments for a variety of health issues. It is projected that the global market for Indonesian traditional medicinal products, of which more than half are herbal medicines, will grow. Unfortunately, there...

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Jonathan, Ernest Suryadjaja, Sulistyo Emantoko D. Putra

DNA polymerase is a remarkably incredible invention in the biotechnology field. Since its discovery, molecular genetic-based research has been growing rapidly. Various methods for molecular-based diagnostics have been developed since. One of which is Loop-Mediated Isothermal Amplification; this method...

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Farizky Martriano Humardani, Lisa Thalia Mulyanata, Lady Theresa Adeodata Tanaya, Risma Ikawaty, Heru Wijono, Hikmawan Wahyu Sulistomo, Dini Kesuma, Sulistyo Emantoko Dwi Putra

Methylation-specific PCR (MSP) is a valuable technique for studying DNA methylation patterns due to its straightforward design and implementation, high sensitivity in detecting methylated DNA, and ability to analyze large sample sizes cost-effectively rapidly. However, researchers need to be cautious...

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Natural Products Isolated from Various Parts of Mangosteen (*Garcinia mangostana* L.) as Therapeutic Agent: A Review

Arif Nur Muhammad Ansori, Yulanda Antonius, Ahmad Affan Ali Murtadlo, Viol Dhea Kharisma, Bayyinatul Muchtaromah, Muhammad Khaliim Jati Kusala, Dora Dayu Rahma Turista, Imam Rosadi, Vikash Jakhmola, Maksim Rebezov, Tarun Parashar, Rahadian Zainul

This review provides a comprehensive analysis of the therapeutic potential of natural products derived from mangosteen (Garcinia mangostana L.). Mangosteen, a tropical fruit native to Southeast Asia, has long been valued for its medicinal properties. The review focuses on the isolation and characterization...

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Identification of ACE1 Inhibitor Derived from Ashitaba's Chalcones: An *in Silico* Approach

Thomas Alessandro, Yulanda Antonius, Ardhia Deasy Rosita Dewi, Sin War Naw, Prita Ayu Kusumawardhany, Lanny Kusuma Widjaja, Hazrul Iswadi, Mariana Wahjudi

The angiotensin-converting enzyme, ACE1, is one of enzymes important to blood pressure modulation. The inhibition of protein responsible for blood pressure regulation, the angiotensin-converting enzyme, ACE1, is considered as a method to alleviate the hypertension condition Ashitaba plant might be potent...

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Patchouli Alcohol Optimization from *Pogostemon cablin* Benth. cv. Sidikalang Leaves Using Response Surface Methodology

Mochammad Firmansyah, Feri Irwansyah, Krisyanti Budipramana, Mochammad Arbi Hadiyat, Ida Bagus Made Artadana, Popy Hartatie Hardjo

The demand for essential oils in the industrial sector continues to increase, proportional to the number of people using them. Pogostemon cablin popularly known as nilam in Indonesia produces patchouli oil with patchouli alcohol as the major compound. Patchouli oil has been used for a long time as perfume...

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Explant surface sterilization protocol for micropropagation *of Amorphophallus muelleri* Blume

Fenny Irawati, Agnes Natalia Wijaya, Anggi Manurung, Michael Anthony Thongiratama, Wina Dian Savitri, Popy Hartatie Hardjo

The success of tissue culture is greatly influenced by the explant surface sterilization technique. The presence of bacterial and fungi contamination, and the occurrence of browning on the explants can interfere with the process of culture propagation. High concentration of sterilant agents will inhibit...

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Utilization of Tempeh Extract as an Organic Supplement

Alternative for Banana Tissue Culture

Alexander Willy Dimaswarabrata, Anastasia Tatik Hartanti, Listya Utami Karmawan

The addition of organic materials to tissue culture media has been known to have a positive impact on plant growth. However, a tissue culture medium utilizing organic supplements originating from Indonesia as its specialty, such as tempeh, has not been discovered. This study aims to determine the effect...

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Syifatul Lutviani, Ita Nur Anisa, Andreanus A. Soemardji

Chronic Obstructive Pulmonary Disease (COPD) is a progressive lung disease characterized by chronic bronchitis, airway thickening, and emphysema. There are several main mechanisms of COPD, namely chronic inflammatory processes in the airways, oxidative stress, and disturbances in the balance between...

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LFER and 3D-QSAR Analysis of Febrifugine Derivatives against *Plasmodium falciparum* FCR-3 Strain

Nur Aina, Tegar Achsendo Yuniarta, Dini Kesuma

Malaria is a serious disease caused by Plasmodium through the bite of the female Anopheles mosquito. Due to resistance to artemisin, a first-line

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Asmiyenti Djaliasrin Djalil, Aqshal Pramudya Susanto, Rizal Nandha Arisugita, Binar Asrining Dhiani, Muhammad Faris Maulidan, Irfan Zamzani

The patient's quality of life may be negatively impacted by the high prevalence of acne vulgaris among adolescents. Acne vulgaris is a skin condition in which hair follicles become clogged with dead skin cells, bacteria, and natural facial oils. It has been demonstrated that acne antibiotics raise antibacterial...

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Formulation of Chewable Gummy Tablet of *Moringa oleifera* L. Leaf Extract Using Combination Kappa Carrageenan and Iota Carrageenan

Nabilaberty Prisma Gemilang, Nikmatul Ikhrom Eka Jayani, Karina Citra Rani

Moringa leaves were the most commonly used part of the Moringa plant because they were rich in nutrients. Moringa leaves extract was developed into a chewable gummy tablet to improve its acceptability. The main component of the chewable gummy tablet was a gelling agent. This study

aims to determine the...

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Stability and antioxidant tests of ethanol extract liposome of moringa leaves (*Moringa oleifera*)

Robert Tungadi, Teti Sutriyati Tuloli, Sri Manovita Pateda

Moringa leaf potentially has an antioxidant effect because it contains Quercetin having poorsolubility in water. Liposomes as carriers of drug compounds can increase the solubility of quercetin through an entrapment system in the lipid bilayer. This study aimed to determine the stability and antioxidant...

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