The Potential of Secondary Metabolites from Indonesian Weeds in Asthma Management

Lathifah Yuliana Hastuti[1](✉) and Dias Setyawan[2]

[1] Universitas Darussalam Gontor, Ponorogo, East Java 63471, Indonesia
lathifahyuliana99@gmail.com
[2] Universitas Negeri Malang, Malang, East Java 65145, Indonesia

Abstract. Managing asthma with clinicaldrugs commonly has some adverse events and drug tolerance. Asthma management with minimal drug side effects is suitable for reducing asthma prevalence. Herbal medicine could apply to mild asthma or as an adjunct to standard asthma management. This study compares the chemical bonds between the secondary metabolites in *Euphorbia Hirta L.* and *Mimosa Pudica L.* with the beta-2 blocker drugs. This research design used computational testing to evaluate secondary metabolites compounds. We tested the binding between secondary metabolite compounds and β2 receptors using the iGEMDOCK application. Beta-2 blocker drugs in this paper were fenoterol hydrobromide (HBr) and salbutamol. In addition, dataanalysis with quantitative descriptive used the findings of the computational test using the docking method. The results indicated that the secondary metabolite compounds in *Euphorbia Hirta L.* and *Mimosa Pudica L.* leaf extracts had similar binding energy to beta-2 blocker drugs. In conclusion, the weed plants of *Euphorbia Hirta L.* and *Mimosa Pudica L.* have the potential to be herbal medicine for individuals with asthma.

Keywords: Weed plants · Herbal medicine · Computational test · *Euphorbia Hirta L* · *Mimosa Pudica L*

1 Introduction

Asthma is a non-communicable disease. The disease is most common in children and is one of adulthood's most common chronic diseases [1]. It is a worldwide well-being issue; mortality was approximately 495,100, and disability-adjusted life year was 22.8 million in 2017. Furthermore, there was more than 1000 death from asthma daily compared to malaria [2].

Asthma fluctuates. It can be the absence of symptoms or not interfering with daily activities. However, there can be exacerbations (worse chronic obstructive pulmonary disease symptoms) and even death [3]. Asthma causes hyperresponsive respiratory tract inflammation. It can cause constriction, edema, and airway mucus hypersecretion in the bronchus [4, 5]. The clinical symptoms include shortness of breath, heavy chest, and allergies[6].

Medically, asthma is a disease that is difficult to cure but controllable, so it does not interfere with daily activities. One way to manage asthma is avoiding precipitating

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factors that cause the onset of asthma symptoms [7]. Inadequate asthma prevention and management potentially increase its prevalence in the future. So it might disrupt the process of child development and the patient's quality of life [3, 8].

Indonesia is a country with abundant natural resources, including plants. It has a very high diversity of flora. In addition, 80% of all the medicinal plants in Southeast Asia are in Indonesia [9]. People in Indonesia still utilize plants as traditional medicine [10]. They have traditionally used natural ingredients to manage various diseases. One of the traditional herbal medicine for asthma is Indonesian weeds which have similar pharmacological effects to asthma drugs. The most beta2 blocker drugs circulating in pharmacies are salbutamol and fenoterol HBr. This study compares the chemical bonds between the secondary metabolites in *Euphorbia Hirta L.* and *Mimosa Pudica L.* with the beta-2 blocker drugs.

2 Method

This research design used computational testing to evaluate secondary metabolites compounds. Data collection of the secondary metabolites of *Euphorbia Hirta L.* and *Mimosa Pudica L.* leaf extracts used the website https://pubchem.ncbi.nlm.nih.gov/. α-amyrin, ascorbic acid, and β-sitosterol were secondary metabolites in *Euphorbia Hirta L.* In addition, there were Betulinol, Cycloartenol, Ferulic acid, Friedeline, Gallic acid, Kaempferol, Linolate, Oleate, and p-coumarate. Furthermore, secondary metabolites in *Mimosa Pudica L.* included mimosine, Rattex, and Spinasaponin. Beta-2 blocker drugs in this paper were fenoterol hydrobromide (HBr) and salbutamol. We tested the binding between secondary metabolite compounds and β2 receptors using the iGEMDOCK application. Furthermore, data analysis with quantitative descriptive used the findings of the computational test using the docking method.

3 Results

Computational docking is the in-silico method. Currently, the pharmacy industry is interested in this research method in searching for potential compounds. The standard drug discovery process takes about 10–16 years, but using the in-silico method, the estimation of time is shorter, and the accuracy of the results is similar to experimental research. Structure-Based Drug Design (SBDD) has a three-dimensional structure of the target drug used as the basis for drug development. Based on the computer-aided drug design (CADD) method. Prediction of the three-dimensional structure of the complex between the target protein and drug candidate plays an essential role in SBDD [11]. Figure 1 shows the docking test using the iGEMDOCK 2.1 software.

The results indicated the binding energy of the secondary metabolite compounds in *Euphorbia Hirta L.* and *Mimosa Pudica L.* in the Beta-2 Blocker ligand. In addition, the binding energy of salbutamol and fenoterol HBr in the Beta-2 Blocker ligand. Mimosine binding energy with beta-2 blocker receptors was 148.6 kcal, Spinasaponin was 126.8 kcal, and Kaempferol was 114.5 kcal. In addition, the binding energy of cycloartenol with beta-2 blocker receptors was 114 kcal, and β-sitosterol was 108.3 kcal.

Compound	Energy	H-S LYS 15	H-S HIS 1093	H-S ASP 1113	H-M VAL 1114	H-M THR 1118	H-S THR 1118	H-S HIS 1178	H-S GLU 1180	H-M CYS 1191	H-S ASP 1192	H-M PHE 1193	H-M THR 1195	H-S THR 1195	H-M SER 1203	H-S SER 1203	H-M SER 1204	H-S SER 1204	H-S SER 1207	H-S ASN 1293
cav6mxt_K5Y-Mimosine-1.pdb	-148,6	-3,5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
cav6mxt_K5Y-Spinasaponin A Methyl Ester-2.pdb	-126,8	-5,2	0	0	0	0	0	0	-5	0	0	0	0	0	0	0	0	0	0	0
cav6mxt_K5Y-fenoterol-1.pdb	-126,4	0	-3,5	-6,9	0	0	0	0	0	-2,5	0	-2,8	0	0	-2,5	-2,5	0	0	-2,5	0
cav6mxt_K5Y-Kampferol-2.pdb	-114,5	0	0	-10	0	0	0	0	0	0	0	0	0	0	0	-2,5	-1,1	-2,2	0	-3,5
cav6mxt_K5Y-cycloartenol-0.pdb	-114	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
cav6mxt_K5Y-beta-sitosterol-2.pdb	-108,3	0	0	0	0	0	0	0	0	0	0	-6	0	0	0	0	0	0	0	0
cav6mxt_K5Y-Betulinol-2.pdb	-104,1	0	0	0	0	0	0	-6,6	0	0	0	-2,7	0	0	0	0	0	0	0	0
cav6mxt_K5Y-alpha-amyrin-0.pdb	-98,4	-3,5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
cav6mxt_K5Y-Oleate-2.pdb	-96,9	-3,1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
cav6mxt_K5Y-Linolate-1.pdb	-93,1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
cav6mxt_K5Y-salbutamol-1.pdb	-92,7	0	0	0	0	0	0	0	0	0	0	-5,5	0	0	0	0	0	0	0	0
cav6mxt_K5Y-Friedeline-1.pdb	-89,4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
cav6mxt_K5Y-gallic acid-2.pdb	-83,1	0	0	-5	-2,4	-0,5	-2,5	0	0	0	0	0	0	0	-2,4	-4,5	0	0	-4,2	-3,5
cav6mxt_K5Y-ferulat acid-1.pdb	-82,3	0	0	-6,9	0	0	0	0	0	0	0	0	0	-2,5	0	-2,5	0	0	0	0
cav6mxt_K5Y-ascorbic acid-0.pdb	-79,2	0	0	0	0	0	-2,5	0	0	0	0	0	0	0	-2,5	-6,9	0	0	-5	-5
cav6mxt_K5Y-P-Cumarate-0.pdb	-73	0	0	0	0	0	0	0	0	0	-1,1	0	-7	-2,3	0	0	0	0	0	0
cav6mxt_K5Y-Rattex-0.pdb	-65,1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-5	-2,8	-2,5	-1,1	-3,5

Fig. 1. Simulation test results of binding energy.

Furthermore, 98.4 kcal was the binding energy of α-amyrin with beta-2 blocker receptors, and 104.1 kcal was Betulinol. Oleate binding energy with beta-2 blocker receptor amounted to 96.9 kcal, Linolate to 93.1 kcal, and Friedeline to 89.4 kcal.

Moreover, the binding energy of gallic acid with the beta-2 blocker receptor was 83.1 kcal, ferulic acid was 82.3 kcal, and ascorbic acid was 79.2 kcal. In addition, p-coumarate binding energy with beta-2 blocker receptors amounted to 73 kcal, and Rattex binding energy to beta-2 blocker receptors amounted to 65.1 kcal. The binding energy of fenoterol HBr with beta-2 blocker receptors was 126.4 kcal, and salbutamol was 92.7 kcal. Thus, based on the computational tests with the docking method, the secondary metabolite compounds contained in *Euphorbia Hirta L.* and *Mimosa Pudica L.* leaf extracts had similar binding energy with beta-2 blocker drugs.

4 Discussion

Airways hypersensitivity begins with the entry of allergens into the body. The APC (Antigen Presenting Cell) will process the allergen. Then, the processed allergens will be communicated to CD + 4 Th2 cells (T helper 2). CD4 + cells are responsible for inflammation in asthma. Furthermore, CD4 + Th2 cells will stimulate B cells to produce IgE (Immunoglobulin E). Then, the formed IgE will attach to the mast cells in the airway. On reexposure by the same allergen, the allergen will be bound to Ig E in the airway. This binding will stimulate the degranulation of mast cells. The mast cells will produce inflammatory mediators. The mediators include histamine, leukotrienes, thromboxane, prostaglandins, and Eosinophil Chemotactic Factor of Anaphylaxis (ECF-A) [2]. These inflammatory mediators will spur the infiltration of inflammatory cells such as eosinophils, lymphocytes, macrophages, neutrophils, and basophils into the bronchial tissues. Infiltration of such inflammatory cells will cause inflammation of the bronchi [3].

Beta2-agonists play a role in airway smooth muscle relaxation. The mechanism stimulates the adrenergic β2 receptors by increasing C-AMP. In addition, beta2-agonists produce functional antagonisms against bronchoconstriction [7, 9, 12]. Short-acting β2 agonist works as a bronchodilator by increasing broncho-selective action, providing a rapid response and excellent protection.

However, Beta2-agonists have several adverse events after long-term use in asthma patients. The events include tremors and tension (especially in the hands), headaches, muscle cramps, and palpitations. In addition, there are tachycardia, arrhythmias, peripheral vasodilation, sleep, and behavioral disturbances. There are also reports regarding paradoxical bronchospasm, urticaria, angioedema, hypotension, and collapse. Furthermore, Beta-2 adrenergic agonists cause hypokalemia at high doses. Pain may also occur during the administration of intramuscular injections. Besides, beta-2 adrenergic agonists can provoke dose drug tolerance compared to medicinal plants. Whereas secondary metabolite compounds in medicinal herbs have similar pharmacological effects in managing asthma symptoms [9, 12].

Secondary compounds in *Euphorbia Hirta L.* and *Mimosa Pudica L.* potentially substitute for beta-2 adrenergic agonists. They have fewer adverse events. However, the disadvantages are a long time in the treatment process. In addition, secondary metabolite compounds in *Euphorbia Hirta L.* and *Mimosa Pudica L.* are not able to bind to the β2 receptor selectively to inhibit the pathophysiology mechanism of asthma [1, 9, 12].

There are also societal problems from the use of beta-2 adrenergic agonists. The selling price of asthma drugs is unaffordable for the lower middle economy. Thus, those economic classes can use the medicinal herbs of *Euphorbia Hirta L.* and *Mimosa Pudica L.*

Herbal medicine could apply to mild asthma or as an adjunct to standard asthma management. People in Indonesia have traditionally used natural ingredients to treat various diseases or as complementary therapies [13]. Some natural compounds in medicinal herbs can have the potential for new drugs in disease management. They can decrease the expression and production of inflammatory mediators and their receptors. In addition, they might reduce the production and activity of messengers and inhibit the expression of transcription factors. So there is a decrease in the release of inflammatory molecules.

Euphorbia Hirta L. is a plant that grows a lot in Indonesia, but its use is still very lacking. Secondary compounds in *Euphorbia Hirta L.* leaf extract could minimize tissue damage or inflammation caused by releasing lipid mediators or leukotrienes, prostaglandins, and histamine in allergic asthma [10, 11]. In addition, the leaves of *Mimosa pudica L.* have several secondary metabolite compounds, such as flavonoids, tannins, alkaloids, glycosides, steroids, and essential oils [14]. Phytochemical screening identified sugars and coumarins in *Mimosa Pudica L.* leaves. There were also alkaloids, sterols, and glycosides. The isolation of the *Mimosa pudica L.* fraction followed by IR and NMR spectra analysis showed the presence of mimosine compounds (5-amino-3-hydroxy-4-oxo-1H(H)-pyridine propionic acid). There were also Spinasterol-α and phenylethylamine derivatives. Besides, *Mimosa pudica L.* leaves contained compounds 5,7,3',4'-Tetrahydroxyl-6-C-beta-D-Glucopy-Ranosyl flavones, 7,8,3',4'-Tetrahydroxyl-6-C-beta-Dglucopyrano-Sylflavone, mimosine, tyrosine, Mimosinamine, and Mimosinic acid [13].

Flavonoids have anti-inflammatory properties through two mechanisms. The first mechanism inhibits arachidonic acid release. In addition, it hinders lysosome enzyme secretion from neutrophil cells and endothelial cells. The second is inhibiting the inflammatory process's proliferation and exudation phases. Inhibition of arachidonic release

from inflammatory cells will result in less availability of arachidonic substrate. Cyclooxygenase (COXs) and Lipoxygenase (LOXs) pathways are the two major enzymatic pathways in arachidonic acid (AA) metabolism. Then, there will be suppression in the number of prostaglandins and leukotrienes. Thus, therapeutic administration of Mimosa pudica L. leaf extract could decrease the expression of iNOS in the bronchioles. The effective dose to reduce iNOS expression by 73.63% was 1000 mg/kg BB [9, 10, 15, 16].

5 Conclusion

The weed plants of *Euphorbia Hirta L.* and *Mimosa Pudica L.* have the potential to be herbal medicine for individuals with asthma.

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