Pharmacogn. Res.
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ORIGINAL ARTICLE

In silico Anti-Preeclampsia Potential of Phytochemical Found in *Ficus elastica*

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ABSTRACT

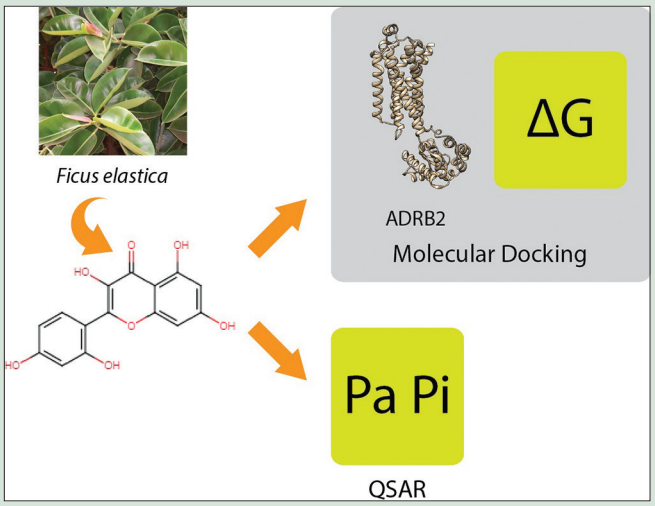
Context: Preeclampsia (PE) is a disorder found in pregnant women characterized by high blood pressure and high protein content in urine. Delivery of the baby and placenta is the most recommended treatment in PE, but treating its symptoms (hypertension) has also been recommended. **Aims:** This study is intended to assess the major compounds found in *Ficus elastica* leaf as anti-PE using an *in silico* approach. **Settings and Design:** All *in silico* analysis was performed under default settings. **Subjects and Methods:** Antioxidant and anti-inflammatory probability values of the five compounds in *F. elastica* leaf are predicted using quantitative structure–activity relationship. The possible binding mode of the compounds is predicted using molecular docking. **Results:** Based on the structural properties, compounds found in *F. elastica* leaf have a high probability activity as an antioxidant and anti-inflammatory. The compounds found in *F. elastica*, especially morin, have the highest binding affinity toward beta-adrenergic receptor 2 (ADRB2) with similar intermolecular interaction with its known inhibitor. **Conclusions:** The compounds found in *F. elastica* may be beneficial for treating PE through its possible antioxidant and anti-inflammatory properties and inhibition of ADRB2.

Key words: *Ficus elastica,* hypertension, molecular docking simulation, preeclampsia, quantitative structure–activity relationship

SUMMARY

- Antioxidant and anti-inflammatory probability values of the five compounds in *Ficus elastica* leaf are predicted using quantitative structure–activity relationship
- The possible binding mode of the compounds is predicted using molecular docking
- The compounds found in *F. elastica* leaf may be beneficial for treating preeclampsia through its possible antioxidant and anti-inflammatory properties and inhibition of beta-adrenergic receptor 2.

Abbreviations Used: ACE: Angiotensin-converting enzyme, ADRB2: Beta-adrenergic receptor 2, ED: Endothelial dysfunction, GCPRs: G-coupled protein receptor, PE: Preeclampsia, QSAR: Quantitative structure–activity relationship, sFlt-1: Soluble fms-like tyrosine kinase-1, SMILE: Simplified molecular-input line-entry system.



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DOI: 10.4103/pr.pr_176_18

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INTRODUCTION

Preeclampsia (PE) is a disorder found in pregnant women characterized by high blood pressure and high protein content found in the urine.[1] PE usually occurs from the 20th week of gestation and affects up to 8% of pregnancies worldwide.[2] PE with another hypertensive-related disease in pregnant women became the major cause of maternal and perinatal mortality.[3] From its pathogenesis perspective, PE starts from the abnormal placental vascular formation, leading to hypoxia and oxidative stress of the placenta.[1] Because of this, the syncytiotrophoblast in the placenta releases extracellular vesicles containing a high content of soluble fms-like tyrosine kinase-1 (sFlt-1) to the maternal bloodstream.[4] The secretion from the placenta caused endothelial dysfunction (ED) results in vasoconstriction of the blood vessel manifested as high blood pressure.[5] Delivery of the baby and placenta is the most recommended treatment in PE, but treating its symptoms has also been beneficial.[6]

The World Health Organization recommends the use of an antihypertensive agent for treating high blood pressure in a pregnant woman with PE.[6] However, the widely used antihypertensive drugs are not available for pregnant women. The common hypertensive drug categorized as angiotensin-converting enzyme (ACE) inhibitor cannot be used safely by a pregnant woman because this type of drug may cause

Cite this article as: Ginting CN, Lister IN, Girsang E, Putri YE, Mutia MS, Purba R, *et al*. *In silico* anti-preeclampsia potential of phytochemical found in *Ficus elastica*. Phcog Res 2019;11:279-82.

fetal development abnormalities.[7] Because of its teratogenicity, another hypertensive agent working indirectly as a blocking beta-receptor was used. Labetalol, a type of beta-blocker drug, was commonly used for the treatment of hypertension in pregnant women.[8] Beta-adrenergic receptor is the most characterized member of G-coupled protein receptor (GCPRs) functioning in various biological functions.

Many plants are used in traditional antihypertensive treatment.[9] Some plants are known to exert its antihypertensive action by affecting the calcium influx in endothelial cell.[10] *Ficus elastica* or rubber fig is a plant widely found in South Asia. The previous study found that *F. elastica* leaf contains various compounds including flavonoid quercetin and myricitrin.[11] Unfortunately, the information regarding the antihypertensive potency of this plant is unknown. With the current development of the bioinformatics tools and database, the prediction of biological activity of compound can be performed *in silico.* Quantitative structure–activity relationship (QSAR) is a method useful for predicting biological activities based on its structural properties.[12] Molecular docking is a method often used to predict the binding mode of compounds toward protein that gives us insights on how the compound may interact with the protein.[13] Therefore, in the present study, using bioinformatics approach, preliminary assessment of *F. elastica* leaf potential as anti-PE was performed.

SUBJECTS AND METHODS

Quantitative structure–activity relationship

The possible biological activity of compounds found in *F. elastica* (afzelin, eleutheroside B, morin, myricitrin, and quercitrin) was calculated using Pass Online web server (http://www.pharmaexpert.ru/PassOnline).[14] PASS Online provides predictions for over 4000 types of biological activities with a mean accuracy of 95%. The input used was a simplified molecular-input line-entry system of every compound that was retrieved from PubChem database. The predicted biological activities returned by Pass Online web server were saved. Pass Online returned the query compounds predicted biological activities as a list of probability estimation expressed as "to be active" (Pa) and "to be inactive" (Pi). The Pa value calculated was based on the compounds' structural similarity toward the known active compound whereas Pi based on the known inactive compound. Thus, the higher the value (Pa > 0.7) is more likely the active query compound because of its shared structural properties with a known active compound.

Molecular docking against beta-adrenergic receptor 2

The receptor used in docking study was beta-adrenergic receptor 2 (ADRB2), a protein targeted in the treatment of hypertension in PE. The three-dimensional (3D) structure data of cocrystallized ADRB2 and alprenolol complex were retrieved from the RCSB database with PDB ID 3NYA. The retrieved receptor data were prepared using AutoDockTools by removing its solvent and any bound ligand except its coenzyme, heme. The compounds mentioned earlier were used as a ligand, and its 3D data were retrieved from the PubChem database. Docking grid box was positioned on the active site of the ADRB2 using its bound ligand (alprenolol) as a reference. The search space dimension was left default (30 Å ×30 Å × 30 Å). The molecular docking was carried using AutoDock Vina.[15] The docking parameter used was left default. To validate the docking result, redocking of crystal-bound ligand was performed. The docked conformation was then compared to crystal conformation to calculate its RMSD using the Hungarian algorithm.[16] The calculated binding affinity of the docked compounds and predicted conformations were saved. The binding conformation of the docked compounds toward ADRB2 was visualized using PyMol.[17] Intermolecular interaction of protein–ligand complex was calculated using PoseView accessible through ProteinsPlus web server (https://proteins.plus/). Intramolecular interactions analyzed in this study were hydrogen bond and hydrophobic interaction.

RESULTS

Biological activity

Antioxidant and anti-inflammatory activities of the compounds found in *F. elastica* leaf were predicted based on its structural properties. All compounds found in *F. elastica* leaf had a high probability as both antioxidant and anti-inflammatory, except eleutheroside B [Table 1]. Myricitrin had the highest probability as both antioxidant and anti-inflammatory (0.93 and 0.76, respectively), whereas eleutheroside B had the lowest probability (0.60 and 0.58, respectively).

Predicted binding affinity and conformation

Molecular docking was performed to predict the possible binding conformation and binding affinity of the compounds found in *F. elastica* against ADRB2. To validate the docking result, the bound ligand of ADRB2, alprenolol, was extracted and docked back to the protein. RMSD of the docked and crystal structure was less than the acceptable cutoff (>2 Å, data not shown). AutoDock Vina was able to recover the crystal conformation. All ligands were successfully docked to receptor. The binding affinity was compared where morin had the highest binding affinity (8.5 kcal/mol) among compounds found in *F. elastica* [Table 2], whereas alprenolol known as a neutral antagonist of ADRB2 had 6.9 kcal/mol.

ADRB2 receptor cavity described as narrow cleft comprised several transmembrane helices (TM).[18] All best-docked ligand conformation was occupied by ADRB2 cavity similar to alprenolol [Figure 1]. Eleutheroside B, morin, alprenolol, and quercitrin formed a hydrogen bond with Asn312 on the TM7 domain [Table 3]. Hydrophobic

Table 1: Biological activity of *Ficus elastica* leaf compounds

Compound	Antioxidant		Anti-inflammatory	
	Pa	Pi	Pa	Pi
Afzelin	0.915	0.003	0.752	0.01
Eleutheroside B	0.6	0.005	0.586	0.035
Morin	0.858	0.003	0.68	0.019
Myricitrin	0.938	0.002	0.762	0.009
Quercitrin	0.919	0.003	0.754	0.01

Table 2: Binding affinity of *Ficus elastica* leaf compounds

Compound	Binding affinity (kcal/mol)
Afzelin	−5.4
Eleutheroside B	−5.2
Morin	−8.5
Myricitrin	−3.0
Quercitrin	−3.8
Bound ligand (alprenolol)	−6.9

Table 3: Hydrogen bond of docked *Ficus elastica* leaf compounds toward ADRB2 residues

Compound	Hydrogen bond
Afzelin	Asp113, Thr195, Ser203, Tyr308
Eleutheroside B	Ser207, Tyr308, Asn312
Morin	Ser204, Tyr308, Asn312
Myricitrin	Asp113, Thr195, Ser203, Ser204, Ser207, Tyr316
Quercitrin	Asp113, Val114, Thr118, Thr195, Ser207, Asn312,
Bound ligand	Asp113, Asn312

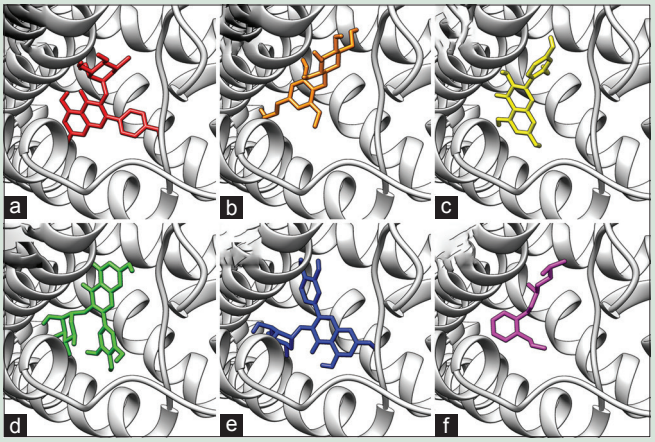

Figure 1: Predicted binding conformation of compounds found in *Ficus elastica* and ADRB2 neutral antagonist toward ADRB2 active site. Binding mode of (a) afzelin, (b) eleutheroside B, (c) morin, (d) myricitrin, (e) quercitrin, and alprenolol (f). The protein showed as cartoon representation. The ligand showed as stick representation with only polar hydrogen showed. ADRB2: Beta-adrenergic receptor 2

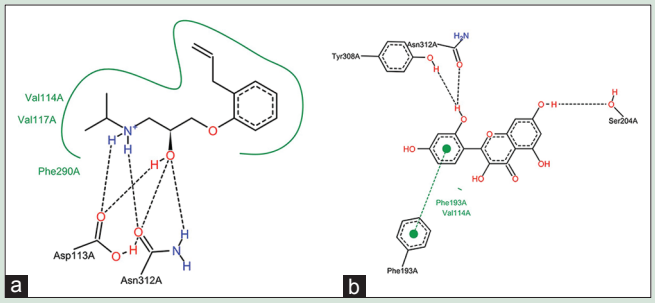

Figure 2: Intramolecular interaction of the highest binding affinity of (a) alprenolol and (b) morin toward ADRB2. Visible difference between compounds was number of hydrogen bond and hydrophobic interaction types. The undirected hydrophobic contact visualized as green lines, directed hydrophobic interaction as green-dashed lines, and hydrogen bond as black-dashed lines. ADRB2: Beta-adrenergic receptor 2

interaction was found enveloping alprenolol [Figure 2a]. A directed hydrophobic interaction (π–π interaction) which was different to alprenolol was found between B phenyl ring of morin and Phe193 residue of ADRB2 [Figure 2b].

DISCUSSION

PE was caused by the developmental defects of the blood vessel found in the placenta, causing an increase of ROS that results in oxidative stress.[19] This condition is an important step in PE, whereas this condition induces the trophoblast to release macrovesicles containing proteins that cause ED.[5] The most common compound found in *F. elastica* leaf was flavonoid compound,[11] a group of phytochemicals known for its free radical scavenging or antioxidant activity. Antioxidant is known to be beneficial for treating oxidative stress[20] and thus may also be beneficial for treating PE. Based on the structural properties, compounds found in *F. elastica* leaf have a high probability activity as an antioxidant and anti-inflammatory, especially myricitrin which has the highest probability as both antioxidant and anti-inflammatory.

Besides immediate delivery of the baby, symptomatic treatment is also recommended in PE.[6] Because of its teratogenicity, ACE inhibitor, a common antihypertensive drug, cannot be used for treating hypertension in a pregnant woman.[7] The previous study found that various phytochemical extracts exert antihypertensive effect by attenuating calcium used in muscle contraction.[10] This effect may be resulted from the inhibition of GCPRs, a protein family involved in calcium release mechanism. ADRB2 is the most characterized member of GPCRs and has been targeted in the treatment of hypertension for a pregnant woman. Based on binding affinity calculated by Vina, morin seems to be a potential binder of the ADRB2. Morin had the highest free energy value among *F. elastica* leaf compounds and was higher than ADRB2 bound ligand. ADRB2 bound ligand was alprenolol, a known neutral antagonist of human adrenergic receptor.[18]

Previous studies reported the interaction profile of agonist, antagonist, and inverse agonist of ADRB2.[21] The study found that Asn312 served as an important residue and needed in ligand binding toward ADRB2 because it was formed by all ligand groups. Several compounds including morin were found to be formed hydrogen bonds toward Asn312. Morin was also found lack interaction with ADRB2 agonist key residues. Interestingly, morin formed a directed hydrophobic interaction with Phe192, whereas alprenolol formed strong undirected hydrophobic contact. Due to its binding affinity and intermolecular interaction, morin may block ADRB2 receptor pocket which reduced its activity, similar with known neutral antagonist. Supported by this, *F. elastica* compound may behave as an antihypertensive agent through attenuating signal transduction by ADRB2.

CONCLUSION

The QSAR analysis showed that *F. elastica* leaf compound may beneficial for treating PE through its possible antioxidant and anti-inflammatory properties, whereas docking analysis showed that morin was a potential antihypertensive agent through the inhibition of ADRB2. Further study is required to assess the actual anti-PE effect of *F. elastica* leaf extract.

Acknowledgments

The authors would like to thank Aretha Medika Utama, Biomolecular and Biomedical Research Center, Bandung, Indonesia, for valuable methodology assistance.

Financial support and sponsorship

This study was financially funded by the University of Prima Indonesia, Medan, Indonesia.

Conflicts of interest

There are no conflicts of interest.

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