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Effect of Phenol and Saponin on Apis Dorsata Forest Honey and Docking Molecule on Preeclamptic Markers

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***Abstract*— Molecular docking is an important computational method for drug design. It can be used to predict receptor binding interactions with ligans. In addition, phenol-derived compounds and Saponins are also reported to have various activities such as anti-hypertensive, anti-inflammatory and anti-apoptosis agents. The purpose of this study is to predict whether the Phenol and Saponin compounds are active as anti-inflammatory agents and also to ensure that the binding interactions are stable before and after the docking calculations. The protocol is carried out in accordance with the standards set by the LPPT-UGM Testing Laboratory. The tools, programs, and applications used in this study were Lenovo IdeaPad Flex 5 Processor, AMD Ryzen 5000 Series 5, AutoDock Tools (v1.5.6), Biovia Discovery Studio, AutodockVina, Swiss ADME, VegaZZ, Pubchem, and the and the pkCSM web server (http://biosig.unimelb.edu.au/pkcsm/). Trans-ADFH three-dimensional structure, as a test compound, and Prednisolone, as a standard compound, were downloaded from https://pubchem.ncbi.nlm.nih.gov/. The phytochemical analysis of ADFH includes phenol and saponin. Structure of PlGF 3D (IRV6) and VEGF (4KZN). Identification of ligands and proteins prepared using Pubchem results of molecular docking between preeclampsia through examination of PlGF and VEGF with phenols and saponins Identification of protein ligands using Pubchem, i.e., PlGF (IRV6) with phenol produced 2 interactions and 2 amino acid residues, while saponins produced 2 interactions and 6 residues. pharmacokinetics and toxicity using Swiss ADME, i.e., phenol and saponins are non-mutagenic to bacteria; the maximum safe dose for humans is 0.54 log mg/kg/day; it does not cause toxicity to the heart; the estimated dose for animals is 2.471 mol/kg; it does not cause allergies; it does not cause liver damage; a dose of 0.288 logμ/L can inhibit the growth of 50% of the protozoa T. Pyformis. The content of phenols and saponins in Apis dorsata forest honey has a high docking score from the original ligand, and -2.85 kcal/mol, while saponins have +2.84, +2.29, and +2.29 kcal/mol values, which are stated to be better results than the original ligands. This means that phenol has a role as a standard drug that can have an effect on lowering PlGF levels for people with preeclampsia. Molecular docking on VEGF identified phenol with scores of -2.88, -2.88, and -2.88 kcal/mol, and saponins have +1.36, +3.46, and +1.36 kcal/mol values, which are stated to have better results than the original ligands. This means that saponins have a role as a standard drug that can have an effect on increasing VEGF levels for people with preeclampsia.**

***Keywords*—First keyword, second keyword, third keyword, fourth keyword, fifth keyword.**

I. INTRODUCTION

Preeclampsia is a severe pregnancy complication characterized by high blood pressure and signs of damage to other organ systems, most commonly the liver and kidneys [1]. Preeclampsia (PE), a hypertensive disorder of pregnancy affecting 2-3% of pregnancies and 15–25% of people with predisposing factors, is a major cause of morbidity and mortality in developed and developing countries. [2]. Preeclampsia (PE) is one of the leading causes of maternal and fetal morbidity and mortality worldwide, associated with gestational age, presentation, and severity of disease [3]. PE is a leading cause of short- and long-term morbidity for infants, including stunted fetal growth and iatrogenic prematurity [4]. Preeclampsia (PE) is associated with placental ischemia, hypertension (MAP), increased cytolytic natural killer cells (cNK), tumor necrosis factor alpha (TNF-α), and mitochondrial reactive oxygen species (mt ROS) [5].

Preeclampsia is caused by vascular failure and spiral artery remodeling, which can harm endothelial cells by inhibiting normal calcium signaling and influencing numerous cytokines and growth hormones. In the trophoblast of the preeclamptic model, mitochondria enlarge in response to cell death. [6]. PE is characterized by the dysregulation of angiogenic factors,

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including Soluble Fms-Like Tyrosine Kinase-1 (sFlt-1). Vascular injury and endothelial dysfunction are made worse by this dysregulation, which lowers VEGF and PlGF levels [7]. It is believed that an angiogenic imbalance brought on by aberrant amounts of placental growth factor (PlGF) and fms-like tyrosine kinase-1 (sFlt-1) is the cause of the vascular inflammatory syndrome in PE [8].

In addition to oxidative stress, immunological dysregulation, vascular endothelial damage, hypoxia, and placental/trophoblastic ischemia, PE's pathogenesis also contributes to maternal morbidity and mortality. Oxidative stress appears to have a major role in preeclamptic individuals' often elevated lipid peroxide and malondialdehyde (MDA) levels. [9]. PE pathogenesis is linked to abnormal trophoblast cell proliferation and death [10].

There is a paucity of pharmaceutical treatments for PE that are safe, effective, and effective [11]. Researchers have been interested in investigating potential treatments for this condition for a long time, focusing on addressing underlying vascular dysfunction and inflammatory responses. This led scientists to hunt for different approaches to enhance PE clinical care. In addition to acute therapy for severe hypertension, best practices are lacking for intrapartum hypertension management [12].

The biomarkers we focused on included mean arterial pressure, proteinuria, malondialdehyde, tumor necrosis factor alpha, soluble Fms-like tyrosine kinase-1, vascular endothelial growth factor, placental growth factor, cysteine aspartic protease 3 (caspase-3), and microvessel density. These markers were chosen to include the vascular, inflammatory, and apoptosis aspects of preeclampsia, with the aim of capturing the multi-faceted nature of the condition. Biomarkers we focus on include MAP, proteinuria, MDA, TNF-α, Sflt-1, VEGF, and PlGF. These markers were chosen to include vascular, inflammatory, and apoptosis aspects of preeclampsia, with the aim of capturing the diverse nature of the condition.

One promising avenue of research involves the use of Apis dorsata honey, a type of honey produced by giant Asian honeybees. Apis dorsata honey has been shown to have a variety of therapeutic properties, including antioxidant, anti-inflammatory, and vasoprotective effects [13].

Our study design involved the induction of preeclampsia-like symptoms in mice using Nω-nitro-L-arginine methyl ester, followed by administration of Apis dorsata honey, nifedipine, or a combination of both. These biomarkers are measured at a designated point in time to see changes and determine treatment. The results of this study have the potential to explain the therapeutic efficacy of Apis dorsata and nifedipine honey, either alone or in combination, in the improvement of preeclampsia.

II. MATHERIAL AND METHODS

A. Materials

A.1 Preparation of ADF

Apis Dorsata Forest The honey used in this study has been examined for phytochemical content at LPPT UGM. Honey is obtained from honey collection farmers who take honey from the Bukit Barisan Lampung National Park Area, which has obtained a distribution permit.

A.2 Apis Dorsata Forest Honey Test

Phytochemical and mineral component tests of honey were carried out at LPPT UGM with the following results: Tanin 0,50% b/b, Flavonoid 0,52% b/b, Alkaloid 0,50, Saponin 2,29, Phenol 1,19, Glukosa 28,86, Water Level 20,28, Natrium, Kalsium, Ferrum, and Zink

A.3 Docking Molecular

Lenovo IdeaPad Flex 5 Processor AMD Ryzen 5000 series 5, AutoDock Tools (v1.5.6), Biovia Discovery Studio, AutodockVina, Swiss ADME, VegaZZ, Pubchem, and the pkCSM web server (http://biosig.unimelb.edu.au/pkcsm/) were the tools, programmes, and applications utilised in this study. Prednisolone was downloaded as the standard compound and trans-EEMP, the test chemical, in three dimensions from https://pubchem.ncbi.nlm.nih.gov/. We retrieved the target gene structures of luxS (PDB ID: ACE2 (1R24) from www.rcsb.org.

B. Method

B.1 Method of phytochemical analysis

Phenol and Saponin are the bioactive substances found in the ADFH. Thin layer chromatography (TLC) is the method used in the phytochemical content test. The ADFH sample is weighed, extracted using 2 ml of methanol, vortexed, and sonicated for 5 minutes. The supernatant is then removed, and the residue is extracted again using 2 ml of methanol, repeating the process for 5 minutes. This protocol is followed in compliance with the standards established by the LPPT-UGM Testing Laboratory. Five minutes of centrifuging are the following step. After placing 10 µl of the supernatant on the F254 silica gel plate, it was placed in a chamber that was saturated with the mobile phase Chorofom-Aceton-formic acid (80:20:0.5). The plate was then eluted to the maximum extent, dried, and then Densito at a wavelength of 348 nm was applied. The average quercetin level was found to be 327.61 in the test findings.

B.2 Preparing the Ligand and Protein

The target proteins used include PlGf with the code 1RV6 and VEGF with the code 4KZN. The structure can be downloaded in .pdb format from the Protein Data Bank (RSCB PDB). The next step involves the creation of ligands for two-dimensional structural tests of Phenol and Saponin compounds. To do this, use SMILES or IUPAC compound names, which can be found by searching for compound names in PubChem. The generated name is then copied and pasted into the VegaZZ program and saved in .pdb format.

Phenol and Saponin, two components of ADFH, are visualised with the Biovia DS Visualizer app (14). PlGF dan VEGF, two molecular indicators of preeclampsia, will be associated with Phenol and Saponin.

The Protein Data Bank (PDB) provided the 3D structure of histamine (2AOU): https://doi.org/10.2210/pdb2AOU/pdb and

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IgE (5MOL): https://doi.org/10.2210/pdb5MOL/pdb, while https://pubchem.ncbi.nlm.nih.gov/compound provided the 3D structure of the quercetin ethanol extract Shame Princess. It is known that the desired gridbox has dimensions of x, y, and z = 40 and values of x = 51.4, y = -23,198, and z = 28,517. Seven is the employed accuracy value (exhaustiveness).

B.3 Step of molecular belaying

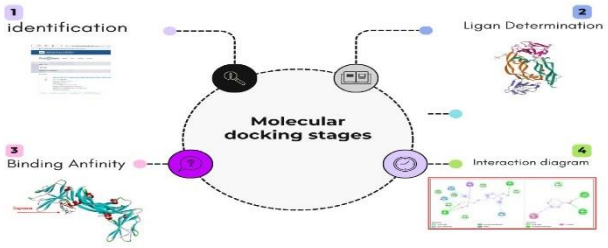


Figure. 1 Using Autodock Vina, Autodock Tools, and Biovia Discovery for molecular docking (15)

B.4 Analysis of Toxicity and Pharmacokinetics

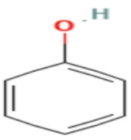
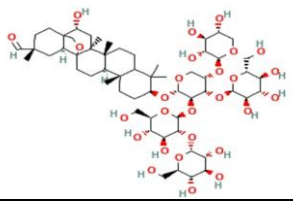
The pkCSM web server was used to predict the pharmacokinetics and toxicity profile of ADFH. Interpretation of the results is done using Max's Ames toxicity. tolerable dose, hERG (the human E ther-à-go-go) I/ II inhibitor, T. Pyriformis toxicity (log ug/L), skin sensitivity, oral rat acute toxicity (LD50), oral rat chronic toxicity (LOAEL), hepatotoxicity, and minnow toxicity (log mM).

III. RESULT

A. The ADFH contains Phenol and Saponin bioactive compounds

Through both positive and negative ionisation modalities, those satu phytochemicals were discovered in the EEMP**.**

Table 1. Phenol and Saponin a phytochemical, in the Apis Dorsata Forest Honey

Phytochemical	**Molecular Formula**	**Molecular Structure**
Phenol	$C_{11}H_{26}N_2O_6$	
Saponin	$C_{58}H_{94}O_{27}$	

B. Molecular docking between ligands Using Pubchem

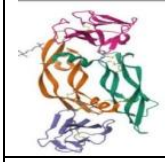
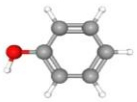
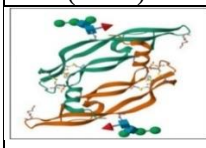
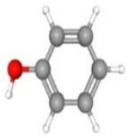
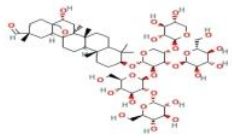
Placental Growth Factor (IRV6)	Phenol	Saponin
		
Vascular Endothelial Growth Factor (4KZN)	Phenol	Saponin
		

Figure. 2 Result of ligands Phenol and Saponin PlGF and VEGF 3D Vizualisation

C. Molecular docking between ligands

D. Phenol and Saponin's molecular characteristics in the ADFG with PlGF and VEGF

Table 3. Molecular properties From Lipinski Ligan

Compound	**Molecular Weight**	**Log P**	**Hydrogen Bond donor**	**Hydrogen Bond acceptor**	**Molar Refraction**	**Compliance RO5**
Phenol	94.11	1.24	1	1	28.46	ya
Saponin	1223.35	4.37	15	27	287.71	ya

E. Prediction of pharmacokinetics characteristic) using PreAdmet

Table 4. Prediction of pharmacokinetics characteristic (adenocarcinoma, Human Intestinal Absorption and Plasma Protein Binding)

Identified Compounds	**$CaCO_2$**	**HIA**	**PPB**
Phenol	24.7123	95.702127	42.439130
Saponin	22.283	90.765	40.765

IV. DISCUSSION

Investigation of the phytochemical content of Apis dorsata forest honey containing phenols and saponins Structure of PlGF 3D (1RV6) and VEGF 3D (4KZN). Identification of ligands and proteins was made using the results of molecular docking Pubchem between preeclampsia by looking at phenols with PlGF and VEGF and saponins with PlGF and VEGF. Using Pubchem, the identification of protein ligands—specifically, PlGF (1 RV6) with phenols—results in 2 amino acid residues and 2 interactions. A dose of -0.198 logμ/L can inhibit the growth of 50% of T protozoa. Pharmacokinetics and phenol toxicity using SwissADME are as follows: it does not cause liver damage or allergies, and the maximum safe dose for humans is 0.54 logmg/kg/day. It also does not impose toxicity on the heart. Apis dorsata forest honey contains phenols,

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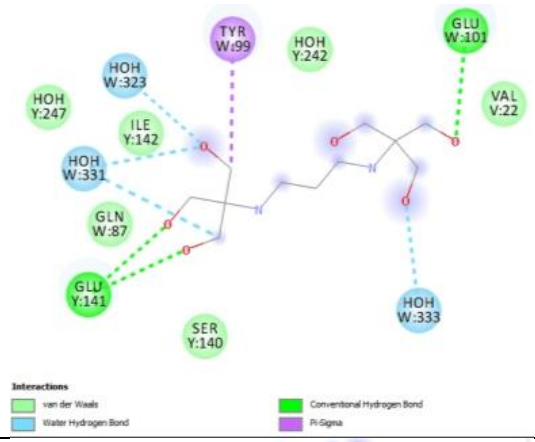
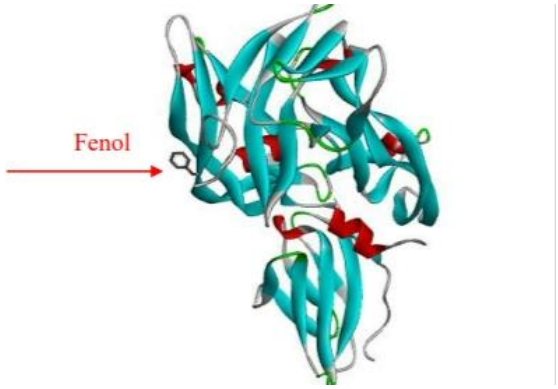
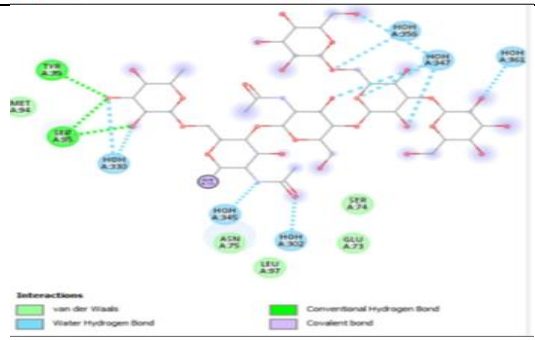
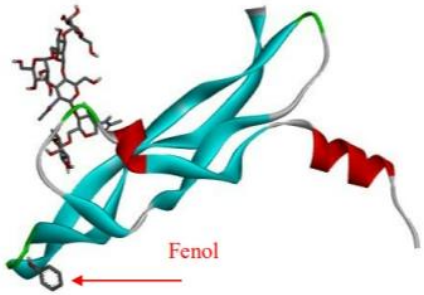
Table 2. 2D and 3D visualization of molecular docking between ligands (Gentiatibetine and Curcomenolacto C) and receptor Preeclampsia

Protein Confirmation	2 D Visualization	3 D Visualization	Interaction	Amino Acid Recidus
Ethanol Extract of Mimosa Pudica linn				
Phenol and Placental Growth Factor (PlGF)			Van der Waal	SER Y 140, GLN W 87, ILE Y 142, HOH Y 247, HOH Y 242, VAL V 22
			Conventional Hidrogen Bond	GLU W 101, GLU Y 141
			Water Hidrogen Bond	HOH W 323, HOH W 331, HOH W 333
			Pi-Sigma	TYR W 99
Phenol and Vascular Endhotelian Growth Factor (VEGF)			Van Der Waals	MET A 94, ASN A 75, LEU A 97, GLU A 73, SER A 74
			Conventional Hidrogen Bond	TYR A 39, SER A 95
			Water Hidrogen Bond	HOH A 330, HOH A 345, HOH A 302, HOH A 356, HOH A 347, HOH A 361
			Covalent bond	ASN A 79

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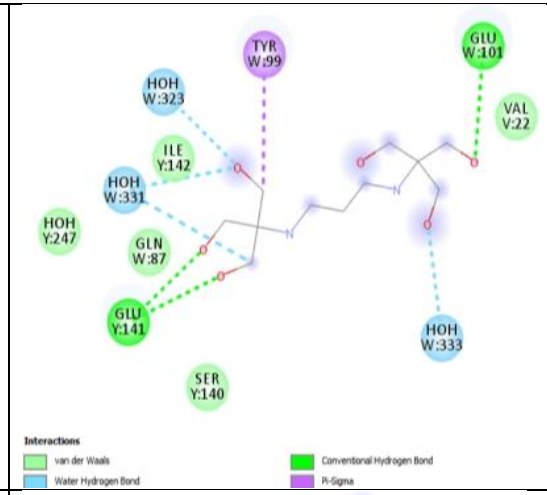
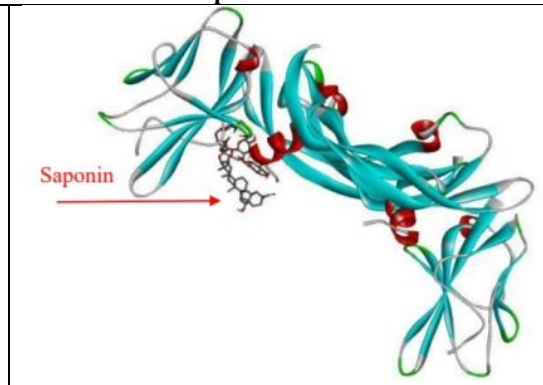
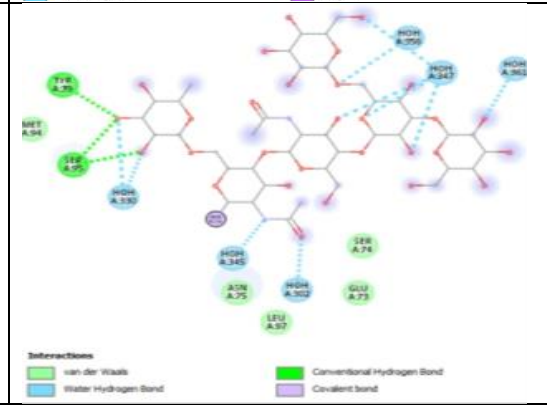
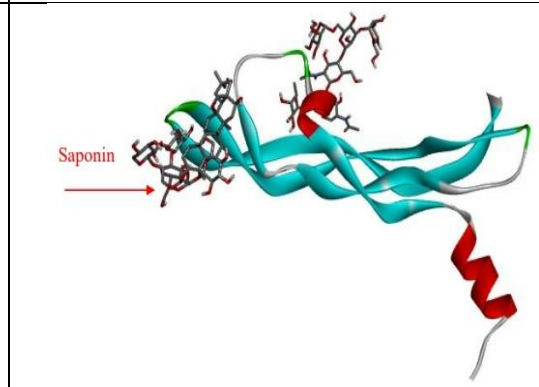
Marker Of Preeclampsia				
Saponin and PlGF			Van Der Waals	ILE Y 142, HOH Y 247, GLN W 87, SER Y 140, VAL V 22
			Conventional Hydrogen Bond	GLU Y 141, GLU W 101
			Water Hydrogen Bond	HOH W 323, HOH W 331, HOH W 333
			Pi-Sigma	TYR W 99
Saponin dan VEGF			Van Der Waals	MET A 94, ASN A 75, LEU A 97, GLU A 73, SER A 74
			Conventional Hydrogen Bond	TYR A 39, SFR A 95
			Water Hydrogen Bond	HOH A 302, HOH A 330, HOH A 347, HOH A 361, HOH A 356
			Covalent Bond	ASN A 75

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saponins, ascorbic acid, and quercetin. By acting as a stabilizer of mast cells and inhibiting the degranulation of mast cells, the anti-inflammatory action of phenol helps control the production of inflammatory mediators such as PlGF and VEGF. It is believed that the action of phenols and saponins will prevent the occurrence of chronic inflammation. In the end, the hope is that honey can treat the occurrence of hypertension and improve the condition of preeclampsia in pregnant women (16).

Other food sources, such as apples, broccoli, garlic, and other fruits and vegetables, all naturally contain phenols, saponins, and quercetin flavonoid molecules. The potential of phenols as anti-inflammatory, antioxidant, and anticancer agents has been studied. (17) According to Singh and Konwar (2012), phenol has a molecular weight of 302.24 g/mol, three hydrogen bond donors, three hydrogen bond acceptors, and a P log of 1.7. Nifedipine, an antihypertensive drug, is used to treat preeclampsia. (18) Nifedipine is a medication commonly used to manage angina and hypertension. The molecular weight of nifedipine is 346.3 grams per mole (g/mol). (19)

Apis Dorsata Forest Honey contains saponins, which have a high docking score comparable to Nifedipine. Saponins are a diverse group of compounds found in various plants, characterized by their soap-like properties. They consist of a glycoside (sugar) part and a non-sugar part (aglycone or sapogenin). Due to their structural diversity, saponins can have different molecular weights. However, here are some examples: Ginsenosides (a type of saponin found in ginseng): Molecular weights can range from around 400 to 1200 g/mol, depending on the specific type of ginsenoside. Diosgenin (a sapogenin found in many plants, often used to synthesize steroid drugs), molecular weight: approximately 414.6 g/mol; Aescin (a mixture of saponins from horse chestnut seeds), molecular weight: varies, but a common form (aescin Ia) has a molecular weight of approximately 1131 g/mol. (17) Because saponins are very widely in their structures, the molecular weight can differ significantly. of -2.85, -2.85, and -2.85 kcal/mol, while saponins have +2.84, +2.29, and +2.29 kcal/mol values, which are stated to be better results than the original ligands. This means that phenol has a role as a standard drug that can have an effect on lowering PlGF levels for people with preeclampsia. Molecular docking on VEGF identified phenol with scores of -2.88, -2.88, and -2.88 kcal/mol, and saponins have +1.36, +3.46, and +1.36 kcal/mol values, which are stated to have better results than the original ligands. This means that saponins have a role as a standard drug that can have an effect on increasing VEGF levels for people with preeclampsia.

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