



In Silico and In Vitro Approach of Preeclampsia Prophylaxis from Water of Kalianda Kopyor

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Abstract

Preeclampsia (PE) stands as a prominent cause of maternal mortality in developing nations, yet a standardized therapy for PE has not been established. Some pregnant women in Lampung have consumed the water of young kopyor coconut fruit from the Kalianda variety (WKK), although its therapeutic effects remain unexplored. This study aimed to investigate WKK phytochemicals through in vitro and silico analyses. Liquid Chromatography-Mass Spectrometry (LCMS) was employed for phytochemical analysis, while an in silico study involved Autodock, Autodock Tools, Autodock Vina, Biovia Discovery Studio 2020, and Open Babel GUI, alongside pharmacokinetics prediction using the pkCSM strategy. The study assessed the inhibitory potential of WKK on Gentiaticetine and curcumenolactone C, targeting the PE ACE2 receptor (1R24) through molecular docking with the 3D structure. Post-docking analysis, including binding affinities, hydrophobic interactions, and pharmacokinetic predictions, was conducted. WKK exhibited relatively low binding affinities for Gentiaticetine (-4.86 kcal/mol), curcumenolactone C (-2.96 kcal/mol), and aspirin (-5.12 kcal/mol). Multiple hydrophobic interactions were observed, such as Van der Waals, Salt Bridge, Conventional Hydrogen Bond, Alkyl, 162, and Lys 129. The receptor IR displayed a high bond-free energy, like aspirin docked with the same gene receptor. Pharmacokinetics predictions indicated that WKK possesses a favorable profile. In conclusion, WKK phytochemicals demonstrated a notable docking score comparable to aspirin, suggesting its potential for preventive therapy use.

Introduction

Preeclampsia (PE) is one of the obstetric disorders that increases maternal mortality in developing countries, which accounts for 15 % of deaths every year and also leads to mortality for fetuses and neonates (World Health Organization, UNICEF, UNFPA, 2019). Approximately 2–8% of total pregnant women

globally tend to suffer PE after 20 weeks of gestation (Poon *et al.*, 2021). Preeclampsia is a heterogeneous condition that can be challenging to diagnose, given the broad spectrum of presentation and the current lack of a robust diagnostic test. The cardinal features of preeclampsia are new-onset hypertension (defined as systolic blood pressure ≥ 140 mm

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Hg or diastolic blood pressure ≥ 90 mm Hg) and proteinuria (300 mg or greater in a 24-h urine specimen) (Qi, Wu, Chen, Wei, & Yao, 2022). Severe pre-eclampsia can be followed by placental abruption, eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count syndrome), and even multiple systemic organ damage (Assersen, Summers, & Steckelings, 2020).

However, a standard therapy for PE has not been established. Recently, it has been reported that 1.5 mg aspirin/day can reduce symptoms and signs of PE. Still, this therapy for long-term periods has negative impacts, including bleeding in late pregnancy (Golyanovskyi, 2021). Another PE treatment uses herbal medicine such as Extra Virgin Olive Oil (EVOO), which contains high monounsaturated fatty acid able to inhibit angiotensin-converting enzyme (ACE), which regulates blood pressure and reduces low levels of nitric oxide and 8-isoprostanes in the urine. Furthermore, some people who drink high olive oil can experience weight gain and nausea (Fitriana *et al.*, 2024). Another natural functional food that is used to reduce high blood pressure is coconut water (Bhagya, Prema and Rajamohan, 2012). A coconut tree, also known as the tree of life, is a tropical plant. It is widely distributed in tropical and subtropical countries, and every part of the coconut tree has beneficial effects on human life (Rao and Najam, 2016). However, the widely used antihypertensive drugs are not available for pregnant women. The common hypertensive drug categorized as an ACE inhibitor cannot be used safely by a pregnant woman because this type of drug may cause fetal developmental abnormalities (Chrismis *et al.*, 2020).

Several bioactive natural products are sources of compounds that have been used either prophylactically or therapeutically to prevent/alleviate diseases (Ahmadu & Ahmad, 2020). The advantage of using natural products is that they are usually well-tolerated with minimal side effects (Cragg & Pezzuto, 2016). Although TCW reduces paw edema and accelerates wound healing in experimental models, the mechanism behind its anti-inflammatory properties has not been determined (Radenahmad *et al.*, 2012), (Rao & Najam, 2016). TCW's reported

anti-inflammatory effects would regulate the expression of inflammation mediators and cytokine-mediated NO production, Nos2 mRNA, and iNOS protein expression in primary rat hepatocytes (Lakshmanan *et al.*, 2020). Given TCW's reported anti-inflammatory and endothelial dysfunction effects, we hypothesized that TCW would regulate the reduction of inflammation mediators and mediated NO production in PE therapy. In addition, water from young Kopyor coconut fruit of Kalianda (WKK) has been drunk by some pregnant women in Indonesia to facilitate the smooth labor process. However, the WKK benefits for their labor process are not supported by scientific data and evidence (Fitriana *et al.*, 2024). Unfortunately, the information regarding the antihypertensive potency of this plant is unknown.

With the current development of bioinformatics tools and databases, the prediction of the biological activity of a compound can be performed *in silico*. Molecular docking is a method for predicting biological activities based on their structural properties (Jiao *et al.*, 2021). Molecular docking is a method often used to foresee the binding mode of compounds toward a protein that gives us insights into how the compound may interact with the protein (Yong, Ge, Ng, & Tan, 2009). Therefore, the objective of this research study was to investigate phytochemicals and molecular docking using a bioinformatics approach; a preliminary assessment of WKK potential as an anti-PE was performed within the WKK (Fitriana *et al.*, 2024).

Material and Method

Coconut fruits (*Cocos nucifera* L var. Kopyor) of the puan Kalianda variety were obtained from Tanjung Anom village, Kalianda district, South Lampung Regency, Lampung Province, Indonesia, and registered in the Indonesian Ministry of Agriculture with number Surat Keputusan Menteri Pertanian Nomor: 96/Kpts/KB.010/2/2017. The coconut fruits were picked up by a 5-month-old and sent to the PT Saraswanti Indo Genetech (SIG), Bogor City, West Java province, Indonesia, for further chemical analysis. The tools, programs, and applications used in this study

were Lenovo YOGA Slim 7i Carbon, Processor Core i7, Chemdraw (v16.0), Python (v3.10.0), Open Babel GUI (v3.1.1.1), MGL Tools or AutoDock Tools (v1.5.7), Biovia Discovery Studio Visualizer 2021 (v21.1), AutodockVina, Command Window, pkCSM web server (<http://biosig.unimelb.edu.au/pkcsm/>). The three-dimensional structure of trans-WKK, as a test compound, and Aspirin, as a standard compound, was downloaded from <https://pubchem.ncbi.nlm.nih.gov/>. Target gene structures of luxS (PDB ID: ACE2 (1R24) were downloaded from www.rcsb.org.

Bioactive compounds of the WKK, such as flavonoids, tannins, saponins, steroids, and triterpenoids, were analyzed using a liquid chromatography/mass spectrometry-quadrupole—time (LCMS/MS-QTOF) device, equipped with the UniFi software (Neacsu *et al.*, 2022). According to the SIG protocol, 1g of the WKK was ultrasonically mixed with methanol solvent for 30 minutes and filtered using a 0.22 μ m PTEF membrane. Furthermore, 10 μ L of the WKK sample was injected into the UPLC system with a C18 Column, 400°C column temperature, and 15°C Autosampler temperature. This LC system used 0.1 % (volume/volume) formic acid in acetonitrile as a mobile phase A and 0.1 % (v/v) formic acid in double-distilled water as a mobile phase B. The flow rate of the LC system was set up at 0.6 mL/min, and the MS settings were the mode of operation, to MSE, ionization: ESI (-)/ESI (+), and acquisition range: 50-1,200 Da. The mass spectra of the bioactive compounds in the WKK sample were identified by comparison to the mass spectra in the library of the UniFi software.

The proteins of WKK (Gentiatibetine, Curcumenolactone C) and aspirin were prepared using the Biovia DS Visualizer application (Trott & Olson, 2010). The preparation of Gentiatibetine, Curcumenolactone C, and aspirin proteins was done by separating the proteins from their native ligands and the residues in their receptors. Then, all files were saved in pdb format. Meanwhile, the ligand preparation was done by optimizing the 3D WKK structure, then the file was saved in .pdb and converted to .pdbqt by Autodock tools (v1.5.7) (Ferdian *et al.*, 2021), while the

validation result was expressed as Root Mean Square Deviation (RMSD) with PyMol 2.4.0. The materials used are the 3D structure of ACE2 (1R24) with Protein Data Bank (PDB) format downloaded at <https://www.rcsb.org/>, which is the main protease of preeclampsia, and the 3D structure of the compound ligands Gentiatibetine and Curcumenolactone C in the Kopyor young coconut water plant, which is downloaded at <https://pubchem.ncbi.nlm.nih.gov/>. Before belaying, set the number of torsions first. Gentiatibetine uses a torsion number of 20, while Curcumenolactone C is 30. The anchorage used in the grid box is center $x = 20,035$, $y = -27,532$, $z = -31.9$, size $x, y, z = 40$. The accuracy value (exhaustiveness) used is 7.

The first step for the research procedure is the preparation of the ligands (Gentiatibetine and Curcumenolactone C), which will be changed in format from .sdf to .pdb in the Open Babel GUI application. Next, to prepare the ACE2 receptor (1R24), open the Biovia Discovery application to clean the water molecules and native ligands on the receptor to get a pure receptor. After the ligand and receptor have been prepared, open the receptor in the Autodock Tools application to add hydrogen atoms with the aim of equalizing the receptor computing temperature, and open the ligand to set the number of torsions, then save. The next step is the anchoring process. To find out where the ligand is attached to the receptor, open the Computed Atlas of Surface Topography of Protein website to see the active binding sites on the receptor and then dock using the blind docking method. Note down all the numbering and formatting in Notepad. After that, combine all the files along with the Autodock Vina application (autodock vina, vina_split, and vina_license) in one folder, then enter the formula for calculations in the Command Prompt, as follows: `D:\>cd file name> vina -config file notepad.txt -log log.txt vina_split -input out.pdbqt` After that, look at the lowest binding affinity value because the smaller the binding affinity value, the stronger the binding ability between the ligand used and the receptor. The final step is visualization of the receptor and ligand in the Biovia Discovery application, both in 2D or 3D, to see the bonds and amino acid residues formed. Figure 1

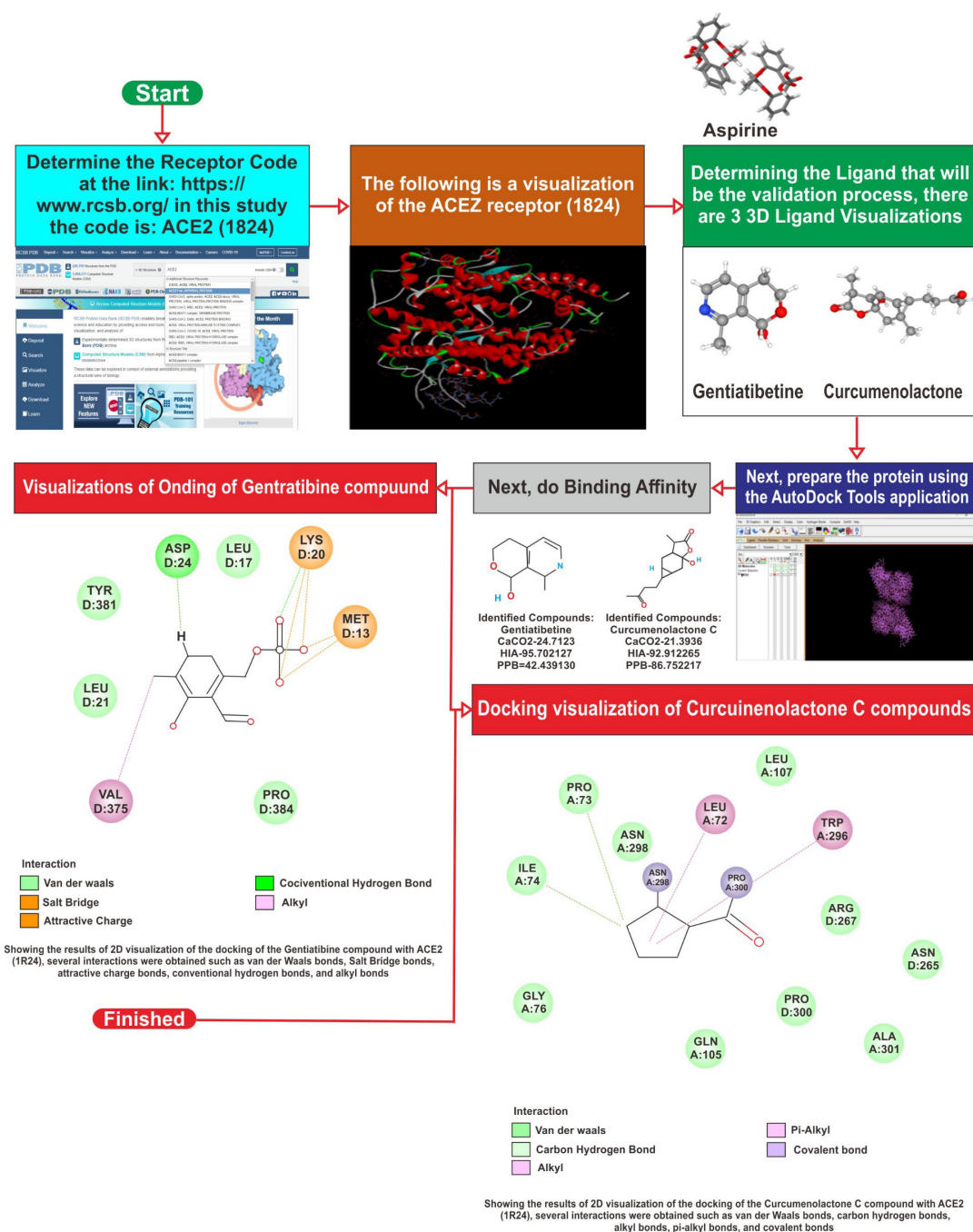


Figure 1. Molecular Docking Using Autodock Tools, Autodock Vina, Biovia Discovery Studio

shows Molecular docking Using autodock.

Prediction of the pharmacokinetics and toxicity profile of WKK was carried out using the pkCSM web server. The results obtained were in the form of ADMET properties represented as absorption, distribution, metabolism, excretion, and toxicity properties,

as well as Lipinski's rule of five.

Result and Discussion

Those two phytochemicals were found in the WKK using positive and negative ionization

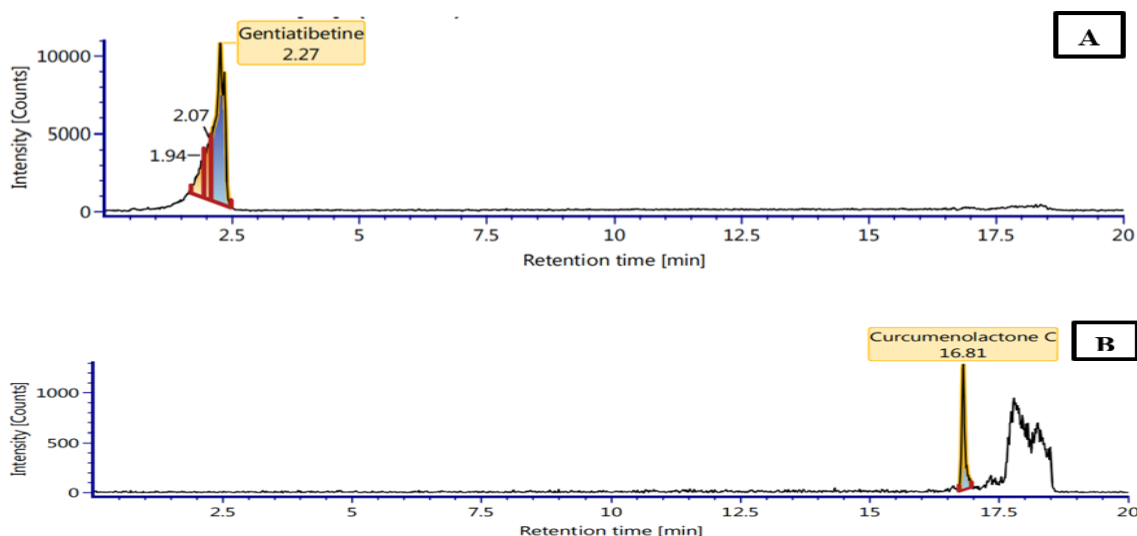


Figure 2. Chromatograms of Phytochemicals in the WKK Sample Were Analyzed Using the LCMS/MS QTOF Method

modes. Figure 2 shows the Chromatograms of phytochemicals in the WKK sample were analyzed using the LCMS/MS QTOF method.

A and B indicated peaks of gentiatibetine and curcumenolactone C phytochemicals, respectively. 10 μ L of WKK samples was injected into the UPLC system with a C18 column and the flow rate in the LC system was 0.6 mL/min. The mass spectra of the bioactive compounds in the WKK sample were identified by comparison to the mass spectra in the library of the UniFI software. Results showed MS (MH) M/Z (ppm) of 2.30 and 4.55 indicated gentiatibetine ($C_9H_{11}NO_2$) and curcumenolactone C ($C_{15}H_{20}O_4$), respectively. In addition, results revealed the percentage of MZ RMS of 7.85% and 6.59% for gentiatibetine and curcumenolactone C, respectively, followed by the retention time of gentiatibetine (2.27 min) and curcumenolactone C (16.81 min). The molecular structure of gentiatibetine ($C_9H_{11}NO_2$) and curcumenolactone C ($C_{15}H_{20}O_4$) is shown in Figure S1. Figure 3 shows the results of 3D ligands visualization.

Table 1 shows molecular docking between ligands (Gentiatibetine and Curcumenolactone C) and receptor Preeclampsia (aspirin).

Figure 4a shows a 2D visualization of molecular docking between ligands (Gentiatibetine and Curcumenolactone C) and receptor Preeclampsia (aspirin), and Figure 4b shows a 3D visualization of molecular

docking between ligands (Gentiatibetine and Curcumenolactone C) and receptor Preeclampsia (aspirin).

In determining the ligand, it is best to comply with the rules formulated by Christopher A. Lipinski, as the name suggests, namely Lipinski's Rule of Five or often known as the Rules of Five (RO5) Lipinski's rules include: molecular weight <500, $\log P$ <5, donor hydrogen bonds <5, and acceptor hydrogen bonds <10.5, shown in Table 1. In addition, results revealed the predicted pharmacokinetic characteristics as shown in Table S2. The selected parameters include human colon adenocarcinoma (Caco2) permeability, Human Intestinal Absorption (HIA), and Plasma Protein Binding (PPB) cells. The ability of drugs to be absorbed in the intestine and the permeability capacity of Caco-2 cells are used to predict drug absorption. HIA is total bioavailability and high absorption determined by the ratio of urine, bile, and fecal excretion. Most anthocyanidin compounds have a high HIA absorption percentage, ranging from 70-100%, except for the chloramphenicol compound. Caco-2 cells are an in vitro model used to determine drug transport through the intestinal epithelial origin of human colon adenocarcinoma. The highest Caco-2 values were found in Gentiatibetine and Curcumenolactone C, namely 24.713 and 21.3936 nm.

In vitro study to identify Gentiatibetine

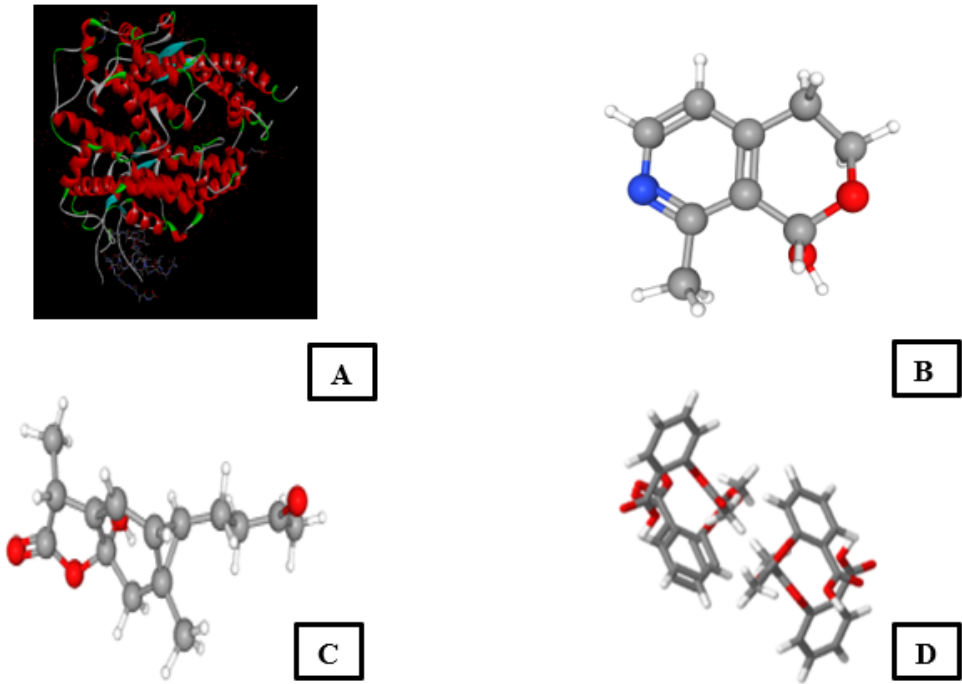


Figure 3. Molecular docking using autodock tools, autodock vina, biovia discovery studio 2020, dan open babel GUI (A) Reseptor ACE2 (1R24), (B) Gentiaticetine, (C) Curcumenolactone C, (D) Aspirine

TABLE 1. Molecular Docking Between Ligands (Gentiaticetine and Curcumenolactone C) and Receptor Preeclampsia (Aspirin)

Protein Confirmation	Interactions	Asam Amino Recidu
Gentiaticetine	Van der Waal Salt Bridge Conventional Hydrogen Bond Alkyl	Leu D-17, Thr D-381, Leu D-21, Pro D-384 LSP-D20, Met D-13 Asp-D 24, Val-D375
Curcumenolactone C	Van der Waals Carbon Hydrogen Bond Alkyl Pi- Alkyl Covalent bond	Leu A:107, ASN A:298, ARG D:267, ASN D:265, Pro A:300, ALA A:301, GLN A:105, GLY A:76. Pro A:73, ILE A:76. Leu A:72 TRP A:296 Asn D-298: Pro A-300
Aspirin	Van Der Waals Salt Bridge Attractive Charge Water Hydrogen Bond Conventional Hydrogen Bond Carbon Hydrogen Bond Unfavorable Acceptor Pi- Donor Hydrogen Bond P- -Pi Stacked Alkyl Pi- Alkyl	GLY 108, SER 297, LEU 113, TRP 141 ATG 267- Conventional Hydrogen Bond ATG 267 HOH 495, HOH 445 ASN 195, TYR 226, THR 110, GLY 109, SER 256 ASP 24, alkyl pada VAL 375 ASP 23 TRP 410-Pi-Pi Stacked TRP 14 -alkyl HS 190 Alkyl-Alkyl

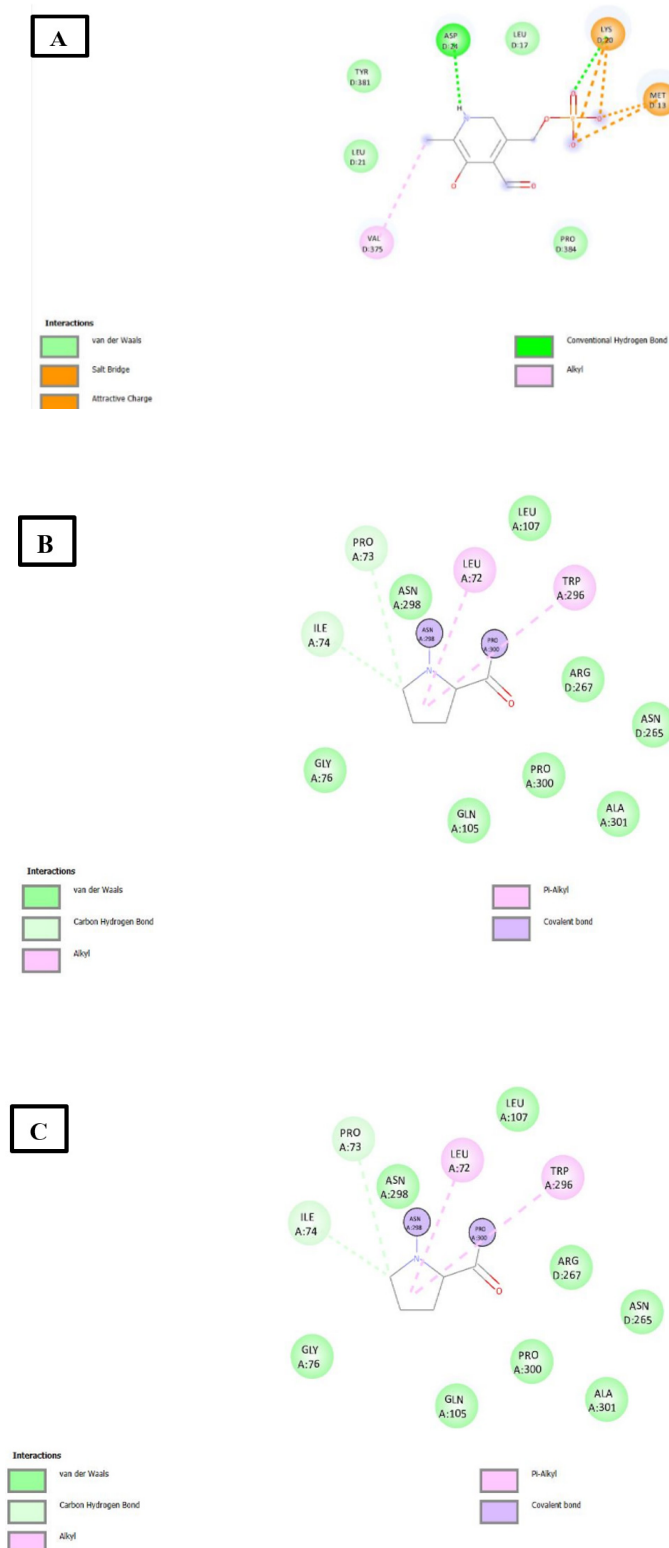


Figure 4. 2D Visualization of Molecular Docking Between Ligands (A) Gentiatibetine, (B) Curcumenolactone C, and (C) Receptor Preeclampsia (Aspirin)

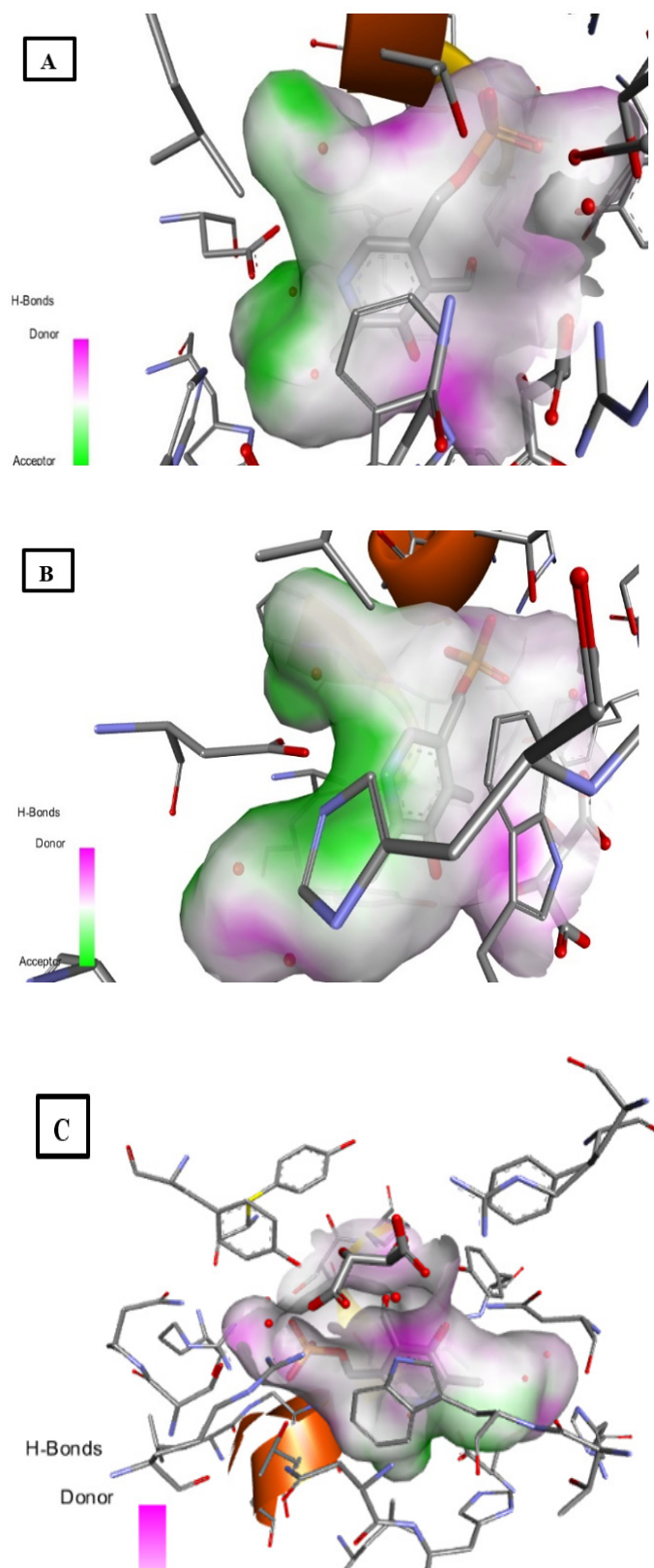


Figure 5. 3D visualization of molecular docking between ligands (A) Gentiatibetine, (B) Curcumenolactone C, and (C) Receptor Preeclampsia (Aspirin)

(alkaloid family) and Curcumenolactone C (terpenoid Family). The materials used are the 3D structure of ACE2 (1R24) identified for ligand and protein preparation using pubchem, result molecular docking between the PE receptor ACE2 (1R24) with gentiatibetine contained 5 interactions and 8 amino acid residues, with Curcumenolactone C sustained 5 interactions and 14 amino acid residues and aspirine 14 interactions and 19 amino acid residues, the pharmacokinetics and toxicity characteristic using PreAdmet to detected CaCO₂, Human Intestinal Absorption (HIA), and Plasma Protein Binding (PPB). Results exhibited that the WKK consists of gentiatibetine and curcumenolactone C. A previous study reported that gentiatibetine, an alkaloid family member, has anti-convulsant activity and brain protective effect (Rahayu & Timotius, 2022). Therefore, this bioactive compound is more likely to be beneficial for preventing PE complications, inhibiting eclampsia development that requires anti-convulsant therapy, such as using MgSO₄ 18. The second bioactive compound in the WKK is curcumenolactone C (a terpenoid family member), which is also found in white turmeric (*Zedoariae rhizoma*) 19 and God's Crown (*Phaleria macrocarpa* Schef) 20, with a hepatoprotective activity. This substance is a lactone and might have crucial bioactive characteristics. Studies have been conducted on the possible anti-inflammatory and antioxidant properties of lactones in general. Curcumenolactone C may be beneficial in lowering inflammation and shielding cells from oxidative damage, both of which are essential for controlling and averting the consequences of preeclampsia (Afrose, *et al.*, 2022). Hemolysis Elevated Liver Enzyme and Low Platelet Count. (HELLP) Syndrome is another PE complication that is characterized by hemolysis, elevated liver enzyme function (transaminase >40 IU/L), and low platelet counts (<150,000/microL) 7. Altogether, it suggests that drinking the WKK potentially inhibits PE complications by protecting the brain and liver from damage.

Fulfillment of the RO5 requirements is intended to help increase the success rate of the experiment (Ferdian *et al.*, 2021). Absorption, distribution, and toxicity parameters were measured with the help of a program accessed

online via the site <https://preadmet.bmdrc.kr/adme/> (Bhat & Chatterjee, 2021). The application can automatically determine expected values when the structure and chemistry of a compound are pulled into a website. Permeability to pass through the testicular epithelium is still considerably small, which can affect bioavailability in the blood. Therefore, both pharmaceutical and structural modifications are needed to increase the permeability properties of the compound. PPB is a small portion of the free drug to be distributed to various tissues (Bhat & Chatterjee, 2021). Binding is described through a percentage from 0-100%, which indicates the strength of the bond. Meanwhile, drug irreversibility can occur due to strong chemical bonds that can cause.

Conclusions

Water of Kalianda Kopyor, a major constituent of Gentiatibetine and Curcumenolactone C, has a high docking score comparable to that of aspirin. Molecular docking of WKK with genes of PE ACE2 (1R24) produced data that predicted substantial binding genes with docking scores of -5.6, -5.0, and -6.5 kcal/mol, respectively. The docking score of aspirin against it was -6.0, -7.5, and -7.0 kcal/mol, respectively. These values indicate that the activity of WKK genes of KPE is like that of the standard drug aspirin. Pharmacokinetics prediction using the pkCSM approach has also shown WKK as an active compound with a good pharmacokinetics profile. Therefore, WKK has the potential to be developed as a nutrition therapy agent against PE. The pharmacokinetics prediction made with the pkCSM approach points to advantageous properties for WKK. However, it should be noted that these predictions are based on computational models and might not fully capture the behavior of the compound *in vivo*. Therefore, to verify these hypotheses and evaluate the actual bioavailability, metabolism, and elimination of WKK in biological systems, experimental pharmacokinetic investigations would be required.

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