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Original Research Article

Molecular Docking Study of Quercetin from Ethanol Extract of *Mimosa pudica Linn* on Asthma Biomarkers

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ABSTRACT

Asthma is a chronic disease affecting approximately 12% of pregnant women, with prevalence rates reported to be as high as 16%. Managing asthma in pregnancy can have implications for the foetus, thus making the choice of treatment crucial. Antihistamines play a key role in managing asthma by addressing allergies and reducing bronchial contractions. *Mimosa pudica* L, a medicinal plant, may offer potential benefits in managing asthma during pregnancy due to its quercetin content. This study aims to determine the quercetin content of the ethanol extract of *Mimosa pudica* (EEMP), and investigate its antiasthmatic activity *in silico*. EEMP was obtained by maceration in ethanol at room temperature for 24 h. The quercetin content was determined by thin-layer chromatography (TLC)-densitometry. The antiasthmatic activity was investigated via molecular docking of the test ligand (quercetin) with asthma biomarkers - histamine and immunoglobulin E (IgE) using various docking tools, including Lenovo Ideapad, AutoDock Tools (v1.5.6), Biovia Discovery Studio, AutodockVina, Swiss ADME, VegaZZ, PubChem, and the pkCSM web server. Quercetin content in EEMP was found to be 327.61 mg/kg. Quercetin demonstrated a high docking score, which was comparable to that of the control ligand prednisolone. Molecular docking interactions of quercetin with IgE showed a docking score of -4.20 kcal/mol, which was more favourable than that of prednisolone. However, for histamine, the average docking score was -7.85 kcal/mol, which was less favourable than that of prednisolone. These findings suggest that quercetin could serve as a potential treatment for reducing IgE and histamine levels in individuals with asthma.

Keywords: Asthma in Pregnancy, Histamine, IgE, *Mimosa pudica* L.

Introduction

Asthma is a chronic illness that affect up to 12% of expectant mothers. Studies indicate that gestational asthma affects around 16% of pregnancies,[1] with some studies reporting a prevalence rate as high as 16%. Treatment of asthma in pregnancy can have implications for the foetus.[2,3] Antihistamines, which can prevent asthma-related allergies and reduce bronchial contractions, are instrumental in asthma treatment.[4] Asthma is characterized as a heterogeneous disease associated with airway hyperresponsiveness and airway inflammation. It is defined by a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough that vary in intensity and over time, along with variable expiratory airflow obstruction.[5]
Asthma management often involves the use of antioxidants, which can neutralize free radicals produced during metabolism and reduce oxidative stress.

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Oxidative stress, resulting from an imbalance between the production of free radicals and the body's capacity to neutralize them, is linked to the pathogenesis and exacerbation of asthma.[6] In this context, antioxidants can reduce oxidative stress and may alleviate asthma symptoms. Pregnant women with asthma may experience foetal growth retardation, leading to both short- and long-term health implications.[7,8,9] Asthma-induced complications during pregnancies may include prematurity, low birth weight, congenital abnormalities, respiratory issues, jaundice, gestational diabetes, intrauterine growth restriction (IUGR), pregnancy-induced hypertension, premature rupture of membranes, placental abruption, and placenta previa.[10]
Limited knowledge exists on plants that could be used in the treatment of asthma in pregnancy. One strategy in addressing this limitation involves the use of bioinformatics systems that can predict biological activity *in silico*. Molecular docking, a computational method used in chemistry, predicts interactions between various molecules, such as proteins and ligands (small molecules). This method involves binding a small molecule to the active site of a protein to assess the likelihood of ligand-protein interaction.[11] This study will employ bioinformatics techniques, including phytochemical analysis and molecular docking, to evaluate the potential of the ethanol extract of *Mimosa pudica* (EEMP) as an agent in the management of asthma in pregnancy.
Treatment of asthma in pregnancy can benefit both mother and child, outweighs the potential risks associated with the use of controller and relief medications. Because asthma exacerbations increase the risk of preterm birth, low birth weight, and foetal mortality, the prescribed treatment often includes inhaled corticosteroids (ICS).[12] Natural pharmacological management strategies, such as using plants containing antihistamines and antioxidants, offer an alternative

approach. One of such plants is *Mimosa pudica* Linn (Mp), known for its anti-asthma properties.[13]

Materials and Methods

Plant collection and preparation of extract

Mimosa pudica Linn was collected from UPT Laboratorium Herbal Materia Medica Batu Malang, Indonesia. The plant material was identified and authenticated at laboratory herbarium with voucher number 074/626/102.20-A/2022.

The plant material was dried, chopped, sliced, and then ground into a powder.[6] The powdered plant material was placed in a glass jar, and then macerated with 96% ethanol at room temperature for 24 h with repeated stirring. The extract was filtered, and the marc was remacerated three times. The extract was concentrated *in vacuo* using a rotary evaporator (RV 10 digital V) at 40ºC to obtained ethanol extract of *Mimosa pudica* (EEMP).

Determination of quercetin content

The quercetin content of *Mimosa pudica* L. was analyzed using thin-layer chromatography (TLC). The EEMP sample was weighed, vortexed, and sonicated for 5 min after being extracted with 2 mL of methanol. The extract was filtered, and the residue was re-extracted for 5 min using an additional 2 mL of methanol. The extraction process followed the guidelines set by the LPPT-UGM Testing Laboratory. Thereafter, the extract was centrifuged for 5 min, and 10 µL of the supernatant was spotted on a F_{254} silica gel plate, which was then eluted in a chromatographic chamber saturated with the mobile phase consisting of chloroform-acetone-formic acid (80:20:0.5). After the plate was fully eluted, it was dried and then analyzed using a Densitometer at 348 nm.

Molecular docking

Molecular docking study was done using a Lenovo IdeaPad Flex 5 with an AMD Ryzen 5000 series 5 processor, along with various software and applications, including AutoDock Tools (v1.5.6), Biovia Discovery Studio, AutodockVina, Swiss ADME, VegaZZ, PubChem, and the pkCSM web server http://biosig.unimelb.edu.au/pkcsm/. Prednisolone was downloaded as the standard compound from PubChem ($C_{21}H_{28}O_5$ | CID 5755), while trans-EEMP, the test compound, was obtained in three-dimensional form from https://pubchem.ncbi.nlm.nih.gov/. The target gene structures, such as luxS (PDB ID: ACE2 (1R24)), were retrieved from the RCSB Protein Data Bank www.rcsb.org

Preparation of ligand and proteins

The target proteins in this study included Immunoglobulin E (IgE), coded 5MOL, and histamine, coded 2AOU3. The structures were downloaded from the Protein Data Bank (RCSB PDB) in pdb format. The two-dimensional structures of the ligands (quercetin and prednisolone) were downloaded from PubChem, saved in pdb format and imported into the VegaZZ application (VEGA ZZ 3.0.5.12) using SMILES tools. The ligands were visualized using the Biovia DS Visualizer software.[15] Quercetin and prednisolone were then docked with two biomarkers of asthma; histamine, and Immunoglobulin E. The 3D structures of IgE (5MOL) and histamine (2AOU) were obtained from the Protein Data Bank (PDB) at https://doi.org/10.2210/pdb2AOU/pdb and https://doi.org/10.2210/pdb5MOL/pdb, respectively. The 3D structure of quercetin was obtained from https://pubchem.ncbi.nlm.nih.gov/compound. The intended grid box dimensions were x = 51.4, y = -23.198, and z = 28.517, with the exhaustiveness set to 7.

Pharmacokinetics and toxicity analysis

The pkCSM web server was used to predict the pharmacokinetics and toxicity profile of EEMP. The interpretation of the results included Max's Ames toxicity test, which assesses mutagenic potential. The analysis also covered tolerable doses, and hERG (the human Ether-à-go-go related gene) I/II inhibition, which refers to the inhibition of potassium channels encoded by hERG I/II. Inhibition of these channels can lead to long QT syndrome, potentially causing fatal ventricular arrhythmias or cardiac toxicity. The study also examined *Tetrahymena pyriformis* toxicity (log µg/L), skin sensitivity, oral acute toxicity in rat (LD_{50}), which indicates the lethal dose that kills 50% of a rodent population, oral chronic toxicity in rat (LOAEL), hepatotoxicity, and minnow toxicity (log mM).

Results and Discussion

In silico analysis revealed binding interactions between quercetin, found in *Mimosa pudica* L and both IgE and histamine. Quercetin (Table 1), a flavonoid known for its antioxidant properties, is found in many plants, including *Mimosa pudica*. Figure 1 presents the 3D visualization of the test ligands and asthma biomarkers (histamine). The ligands interacted with the amino acid residues of IgE and histamine through hydrogen and non-hydrogen bond interactions. The interactions of the ligands and asthma biomarkers are shown in Table 2.

The molecular docking between quercetin and histamine displayed 18 amino acid residues and 6 interactions with an average docking score of -7.85 kcal/mol, which was less favourable compared to that of the control ligand (prednisolone). On the other hand, the molecular docking between quercetin and IgE revealed 9 amino acid residues and 5 interactions with a docking score of 4.20 kcal/mol, which was more favourable than prednisolone. A dose of 0.288 log µg/L was sufficient to inhibit the growth of 50% of the protozoa *Tetrahymena pyriformis*. Pharmacokinetic and toxicity analysis using SwissADME indicated that quercetin does not cause liver damage or allergies, with a maximum safe dose for humans of 0.499 log mg/kg/day. Additionally, quercetin does not exhibit cardio toxicity.

Administration of *Mimosa pudica* L containing crocetin, ascorbic acid, and quercetin, may help manage asthma.[14,15] Quercetin exhibits its anti-inflammatory properties, by stabilizing mast cells and inhibition of mast cell degranulation, which contribute to the regulation of inflammatory mediators such as histamine, cytokines, and chemokines.[16,17] Quercetin's actions may prevent chronic inflammation, potentially improving pregnancy-related asthma by reducing reactive oxygen species (ROS) and acting as a bronchodilator on the mother's bronchi, which may enhance both maternal asthma and foetal development.[18,19,20]

Quercetin is abundant in apples, particularly in the skin, where the levels range from 1.0 to 4.5 mg per 100 g, while the flesh contains 0.2 to 0.6 mg per 100 g. Oranges also contain quercetin, with levels ranging from 0.2 to 0.5 mg per 100 g. *Mimosa pudica* Linn has higher quercetin content (327.61 mg per kg) compared to apples and oranges. Quercetin's potential as an anti-inflammatory, antioxidant, and anticancer agent has been widely studied. Study revealed that quercetin (molecular weight = 302.24 g/mol) has three hydrogen bond donors, three hydrogen bond acceptors, and a log P of 1.7. Prednisolone (molecular weight = 360.44 g/mol), a synthetic corticosteroid used to treat various conditions, including arthritis, asthma, and allergies,[18] has three hydrogen bond donors, three hydrogen bond acceptors, and a log P of 1.63.[19] Table 3 presents the predicted toxicity results for quercetin. AMES toxicity, a widely used method for initial screening of mutagenicity in bacteria, shows a result of "No," indicating that quercetin is not mutagenic. The Maximum Tolerated Dose (MTD) for humans was found to be 0.499 log mg/kg/day, placing it in the high category (≥ 0.477 log mg/kg/day) and representing the estimated safe dosage for Phase I clinical trials. The human Ether-à-go-go (hERG) I/II inhibitor test, which assesses the potential inhibition of potassium channels (a condition that can lead to long QT syndrome and fatal ventricular arrhythmias or cardiac toxicity), also shows a "No" result, indicating that quercetin does not inhibit these channels. Both Oral Rat Chronic Toxicity (LOAEL) and Hepatotoxicity tests predicted that quercetin does not induce liver damage, as evidenced by the "No" result. Lastly, minnow toxicity, based on the lethality to Flathead minnows, yielded an LC_{50} value of 3.721 log Mm, indicating the concentration at which 50% of the minnow population is affected.

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Table 1: Quercetin, a phytochemical, in the ethanolic extract of Mimosa Pudica Linn

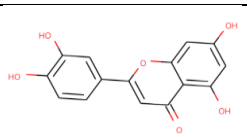
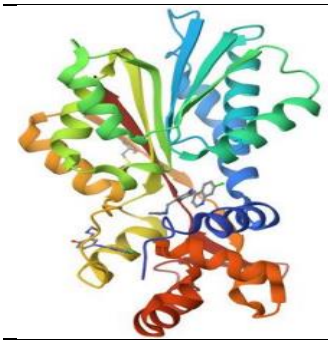
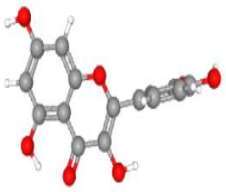
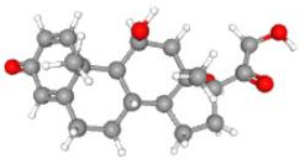
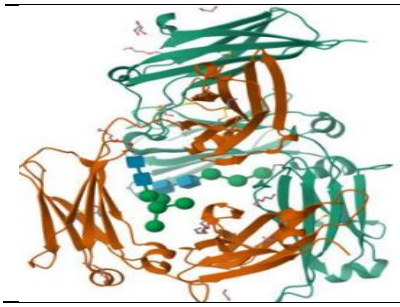
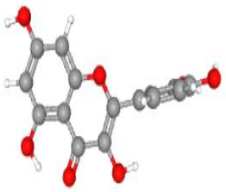
Phytochemical	**Molecular Formula**	**Molecular Structure**
Quercetin	$C_{15}H_{10}O_7$	
Histamin (2AOU)	Quercetin	Prednisolone
		
IgE	Quercetin	Prednisolone
		

Figure 1: 3D Vizualisation of Ligands (Quercetin and Prednisolone) and Proteins (Histamine and IgE)

Table 3: Predicted Toxicity of Quercetin from *Mimosa pudica* Linn

No	**Model Name**	Outcome
1	AMES Toxicity	No
2	Hepatotoxicity	No
3	Minnow toxocity (Mm)	3.721
4	Max. tolerable dose in humans (mg/kg/day)	0.499
5	Acute oral toxicity in rats (mol/kg)	2.471
6	Chronic oral toxicity in rats (mol/kg)	2.612

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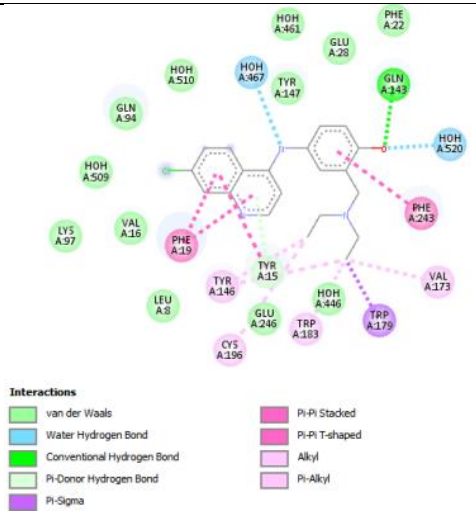
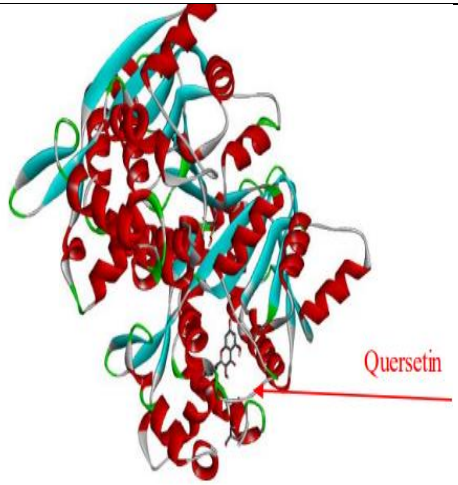
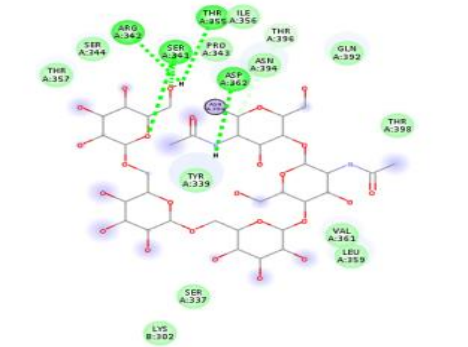
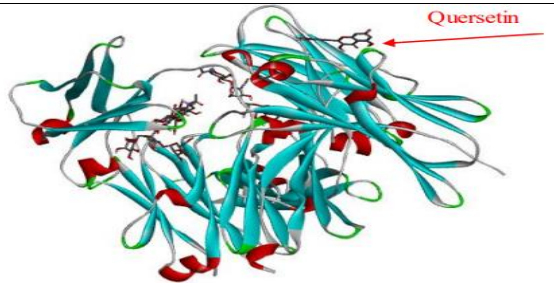
Table 2: 2D and 3D visualization of molecular docking interactions between ligands (*Quercetin* and Prednisolone) and asthma biomarkers (Imunoglobulin E and Histamine)

Ligand-Protein	2D Visualization	3D Visualization	Interaction	Amino Acid Residue
Quercetin and Histamine			Van der Waals	Lys 97, HOH 509. GLB 97, HOH 46, TYR 147, GLU 28, PHE 22, VAL 16, LEU 8, GLY 246, HOH 446,
			Salt Bridge	Lsp 20, Met 13
			Conventional Hydrogen Bond	GLN 143
			Alkyl	VAL 173
			Pi-Alkyl	Trp 183
			Covalent bond	VAL 81, ILE 83
Quercetin and IgE			Van Der Waals	ILE 356, ASN 394, GLN 392, LYS 302
			Conventional Hydrogen Bond	GLN 143
			Alkyl	VAL 173
			Pi-Alkyl	Trp 183
			Covalent bond	VAL 81, ILE 83
Prednisolone and IgE			Van Der Waals	Gly 108, Ser 297, Leu 113, Trp 141
			Salt Bridge	atg 267
			Attractive Charge	Atg 267
			Water Hydrogen Bond	Hoh 495, Hoh 445

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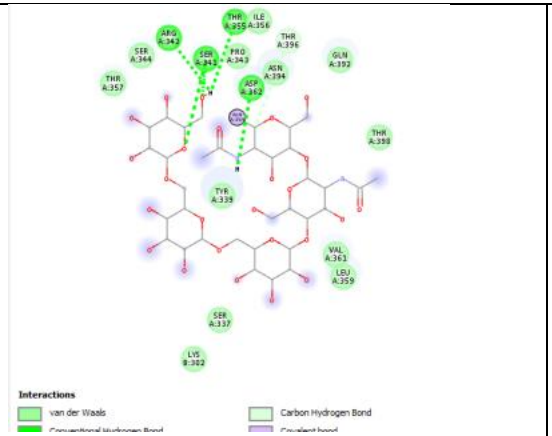
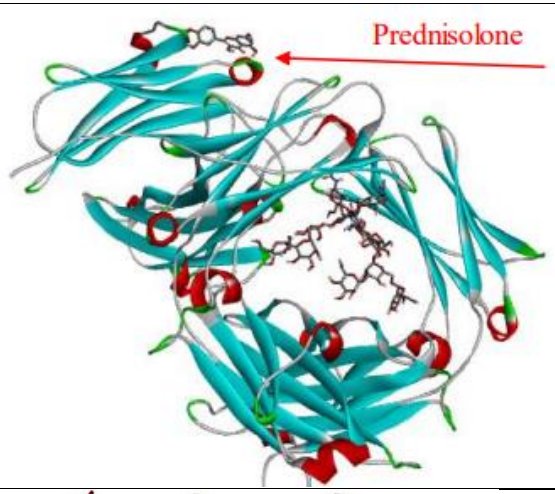
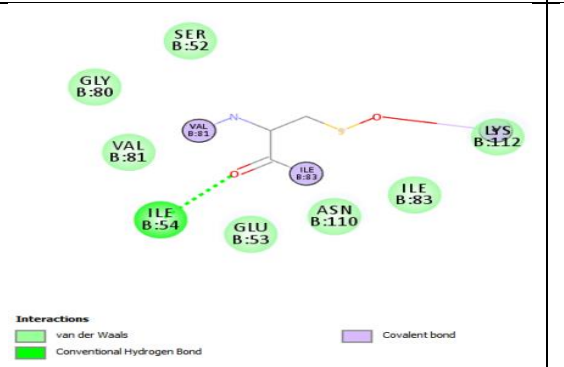
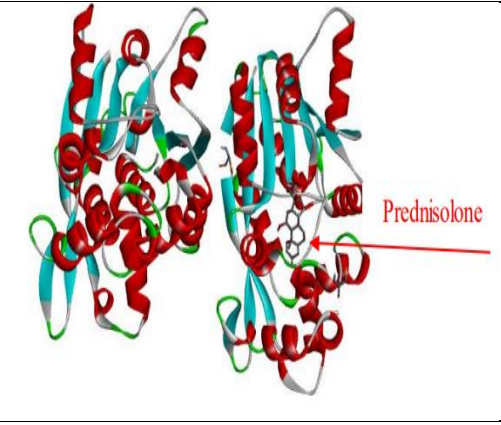
			Conventional Hydrogen Bond	Asn 195, Tyr 226, Thr 110, Gly 109, Ser 256
			Carbon Hydrogen Bond	Asn 24, Val 375
			Unfavorable Acceptor	Asp 23
			Pi-Donor Hydrogen Bond	Trp 410
			Pi-Pi Stacked	Trp 14
			Alkyl	Hs 190
			Pi-Alkyl	Alkyl-Alkyl
Prednisolone and Histamine			Van Der Waals	Gly 80, Ser 52,Val 81,Glu 53, Asn 110, Ile 83
			Salt Bridge	atg 267
			Attractive Charge	Atg 267
			Water Hydrogen Bond	Hoh 495, Hoh 445
			Conventional Hydrogen Bond	Ile 54
			Carbon Hydrogen Bond	Val 81, Ile 83

Conclusion

The ethanol extract of *Mimosa pudica* L. contains quercetin, which has a high docking score comparable to that of prednisolone. Molecular docking studies on EEMP showed score of -4.20 kcal/mol for IgE, indicating that its docking performance is comparable to that of the original ligand. In contrast, the docking scores for histamine, which were reported to be lower than those of the original ligand, were -7.93, -7.92, and -7.69 kcal/mol. This suggests that quercetin may be a viable candidate for a drug that could help lower IgE and histamine levels in people with asthma. To validate these findings, further *in vivo* testing using animal models is necessary.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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