Swietenia mahagoni Leaves Ethanolic Extract: *In vitro* anti-Oxidant Activity, Active Compound Identification and *in silico* Prediction as AKT-1 and MDM2 Protein Inhibitor

Sapti Puspitarini[1]*, Mohammad Budiyanto[1], Muhammad Arif Mahdiannur[1], Roihana Waliyyul Mursyidah[1], Ertika Fitri Lisnanti[2], Fasih Bintang Ilhami[1]

[1]Science Education Study Program, Faculty of Mathematics and Natural Science, Universitas Negeri Surabaya, Surabaya, Indonesia
[2]Animal Husbandry Study Program, Faculty of Agriculture, Islamic University of Kadiri, Kediri, Indonesia

ABSTRACT

The strong correlation between traditional practices and the pharmacological properties of these plants supports their continued use in treating various health conditions. This study evaluated and predicted the active compound in the ethanolic extract of *Swietenia mahagoni* leaves and their potency for inhibiting cancer cell growth. The analysis included measuring DPPH free radical inhibition, total phenolic and flavonoid content, drug-likeness evaluation, and molecular docking studies. Findings suggest that the ethanolic extract of *S. mahagoni* leaves ethanolic extract exhibits antioxidant properties due to its content of phenolic and flavonoid compounds such as Quercitrin, (+)-ar-Turmerone, and Hyperoside, which also meet Lipinski's criteria. Additionally, these compounds might act as inhibitors of MDM2 or AKT-1, potentially blocking MDM2 and AKT-1 and inducing apoptosis in cancer cells. Further research should be conducted in vitro to validate the activity of the studied compounds.

Keyword: Anticancer, Insilico, Plant-based medicine, Secondary metabolite, *Swietenia mahagoni*

1. INTRODUCTION

The incidence of cancer is increasing rapidly, fueling the search for new treatments. Although progress in cancer research is accelerating, only a few drugs make it through clinical trials successfully [1,2]. Cancer cells are categorized according to their origin or the genetic mutations involved in their growth [3,4]. Effective treatment usually requires a combination of drugs designed to target the unique characteristics of the cancer cells. As a result, there is growing interest in developing novel anticancer therapies from natural sources [5–7].

Traditional healthcare practices include a diverse array of methods, prominently featuring plant-based remedies used alone or in combination to treat diseases in humans and animals globally [8]. These practices span various traditional systems such as ancient Korean, Malay, Chinese and Indian and African medicines [9]. Indonesian folk medicine is noted for its distinctive diagnostic and treatment methods, leveraging the country's rich biodiversity and diverse indigenous cultures. For centuries, Indonesian communities have relied heavily on plant-based remedies, with about 85% of their healthcare formulations derived from plants [10].

The popularity of herbal remedies is due to their cultural acceptance, cost-effectiveness, perceived efficacy, and minimal side effects [11,12]. Recent research has focused on analyzing medicinal plants recommended by traditional practitioners to identify bioactive compounds and enhance drug discovery. The strong correlation between traditional practices and the pharmacological

***Corresponding author: Sapti Puspitarini**
saptipuspitarini@unesa.ac.id
Received: 16/08/2024 Accepted: 21/09/2024.
DOI: https://doi.org/10.35516/jjps.v18i3.3169

properties of these plants supports their continued use in treating various ailments [13,14]. Additionally, conducting drug-likeness analysis is essential for discovering high-quality drug candidates from herbal medicine, as it helps avoid unnecessary biological testing and clinical trial expenses [15,16].

Swietenia mahagoni is utilized as a medicinal plant in various regions, including India (within the Ayurvedic system), several African countries, and in Indonesia and Malaysia. Traditionally, it is used to treat malaria, hypertension, diabetes, and diarrhoea, and serves as an antipyretic, bitter tonic, and astringent[17]. The pharmacological properties of *S. mahagoni* include antimicrobial, anti-inflammatory, hepatoprotective, neuropharmacological, anti-diabetic, immunomodulatory, and anticancer activities [18]. However, the anticancer mechanism of this plant has yet to be widely studied. Thus, this study evaluated and predicted the active compound that is contained in *S. Mahagoni* ethanolic extract and their potency for inhibiting cancer cell growth.

2. MATERIAL AND METHODS

2.1 *Swietenia mahagoni* leaves extraction process

Powder dried leaves of *S. mahagoni* was obtained from Materia Medica Batu, Batu, Indonesia. Extraction processes were conducted at Pharmacology Laboratorium, Universitas Brawijaya, Malang, Indonesia using ethanol as the solvent. Powder leaves were macerated in ethanol with ration 1:10 w/v (g/mL) for 24 hours. The macerated was filtered using filter pape. The extract was dried using rotary evapotaror in temperature 80°C.

2.2 Antioxidant analysis from the extract

The antioxidant activity which produced by extracts was analysis with 2,2-diphenyl-1-picrylhydrazyl (DPPH) [1] free radical. In this study, a freshly prepared DPPH solution (0.2 mM) in 100% ethanol was employed. *S. mahagoni* extracts and the equivalent amount (100 µL) of the DPPH solution were combined in a microplate (Costar 96-well plate). The reaction mixture was let remain in the dark at room temperature (25 °C) for 30 minutes. For the control, the same amount (100 µL) of ethanol and DPPH solution were combined. Using a microplate spectrophotometer (SPECTROstar Nano - BMG LABTECH, Germany), the absorbance value of the reaction mixtures was determined at 517 nm. Using Equation 1, the DPPH radical scavenging activity was determined. The IC50 value was calculated by interpolating the fifty values to the linear regression equation (R2 > 0.99) derived from the inhibition curve.

$$\text{DPPH inhibition (\%)} = \left(\frac{\text{AB} - \text{AS}}{\text{AB}}\right) \times 100 \qquad \text{Equation (1)}$$

where, AB is absorbance of blank; AS is absorbance of the sample

2.3 Total flavonoids assay

The colorimetric evaluate with aluminium chloride was carried out to determine the total flavonoids content [1]. The standard of reference was quercetin with concentration of 0.0125, 0.025, 0.05, 0.1, 0.2, 0.4 mg/mL. The 0.001 g/mL of *S. mahagoni* ethanolic extract was used for sample. The 150 µL of 96% ethanol solution was added after about 50 µL of *S. mahagoni* ethanolic extract or standard was added to 10 µL of aluminium chloride (10% w/v). Next, 10 µL of 1M concentration sodium acetate (Sigma) was added to the solution. For forty minutes, the solution was kept out of the light and incubated at room temperature. At $\lambda = 405$ nm, the absorbance was measured with a BioTek ELx808 ELISA reader. The total flavonoid concentration was reported as mg QE/g w.b. of dry extract, which is comparable to quercetin, according to the quercetin standard curve equation.

2.4 Total phenolic content analysis

The Folin-Ciocalteau procedure was used to analyze the total phenolic content [19]. The standard of reference was gallic acid with concentration of 0.0125, 0.025, 0.05, 0.1, 0.2, 0.4 mg/mL. The 0.001 g/mL of *S. mahagoni* ethanolic extract was used for sample In a 96-well microplate, 30 µL of 1.0 N Folin-Ciocalteu reagent was

combined with 60 µL of samples (standard and *S. mahagoni* ethanolic extract), and the mixture was incubated for 5 minutes. Next, 150 µL of a 20% sodium carbonate solution was added, and the mixture was allowed to sit at room temperature for 40 minutes in a dark area. After 8 minutes of centrifugation (1600×g), the absorbance of the the suspension was measured using a Microplate Reader at 730 nm. Gallic acid (mg GAE/g w.b.) was used in a standard curve to determine the samples' total phenolic content.

2.5 Screening and identification of bioactive compounds in phytochemicals

The phytochemical content in seagrass extracts was analyzed using Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) with a Q-exactive model from Thermo Fisher Scientific. 1400 µL of modified solvents (water, 50% ethanol, or 100% ethanol) were used to dissolve 100 µL of *S. mahagoni* extract. Samples were introduced into the LC-HRMS device after being filtered using a 0.22 m RC minisart. A total of ten milliliter samples will be automatically processed using a hypersil gold aQ 50 × 1 mm × 1.9 column at positive polarity conditions, with a flow rate of forty liters per minute and an oven column temperature of thirty degrees Celsius. The elution gradient will be as follows: 5% B for two minutes, 60%-95% B for fifteen to twenty-two minutes, and then 5% B for thirty minutes. Utilizing the Compound Discoverer 3.1 program, which is based on the mzcloud, the chromatogram data produced by the injection procedure will be examined to identify the compounds [19]

2.6 ADME and Drug-Likeness Analysis

The online web server pkCSM (http://biosig.unimelb.edu.au/pkcsm/) can be utilized to predict ADME (absorption, distribution, metabolism, and excretion), while the web server at (https://tox-new.charite.de/protox_II/) is available for predicting toxicity and evaluating the Lipinski Rule.

2.7 Ligand and protein structures preparation

The ligands used for docking analysis were Quercitrin, (+)-ar-Turmerone, Hyperoside, an imidazole (an MDM2 inhibitor) and AZD5363 (an AKT-1 inhibitor). The 3D structures of three ligands (Quercitrin, (+)-ar-Turmerone, and Hyperoside) were obtained from PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The 3D structure for imidazole was obtained from native ligand in MDM2 protein (PDB ID, 4OQ3) from PDB database. The 3D structure for AZD5363 was obtained from native ligand in AKT-1 protein (PDB ID, 4GV1) from PDB database. The proteins were cleaned using BIOVIA Discovery Studio software.

2.8 Ligand docking studies

AutoDock Vina integrated in PyRx 0.8 was used to analyze interactions between ligands and proteins. In order to assess binding affinities and elucidate molecular pathways, the docking approach was applied. In order to execute docking, ligands were made into flexible molecules and receptors into stiff molecules inside the active site. By using BIOVIA Discovery Studio, docking and binding interaction results were examined.

3. RESULT

3.1 Antioxidant activity of *S. mahagoni* ethanolic extract

The antioxidant activity some compounds could be determined by their ability to inhibit free radical, such DPPH free radical. *S. mahagoni* ethanolic extract showed their ability to inhibit DPPH free radical manner by concentration (Table 1). Interestingly, about 25 ppm of *S. mahagoni* ethanolic extract, DPPH free radical was inhibited around 50%. This early finding has positive value for *S. mahagoni* ethanolic extract for their bioactivity.

Table 1. Antioxidant activity analysis from the *S. mahagoni* ethanolic extract

Concentration (ppm)	DPPH inhibition (%)
0.39	2.32 ± 0.11
0.78	4.30 ± 1.25
1.56	7.03 ± 0.35
3.13	11.12 ± 0.62
6.25	18.42 ± 0.77
12.50	32.47 ± 0.85
25	50.14 ± 0.11
50	84.99 ± 1.30

3.2 Total phenolic and Total flavonoid of *S. mahagoni* ethanolic extract

Phenolic and Flavonoid are secondary metabolites which support pharmaceutical effect in plant, as well as *S. mahagoni* ethanolic extract. Total flavonoid and phenolic content could be imaging the pharmaceutical effect the plant. *S. mahagoni* ethanolic extract measured contain TFC 458.91 ± 21.60 (mgQE/g w.b) and TPC 299.90 ± 14.28 (mgGAE/g w.b) (Table 2)

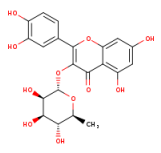
Table 2. Total phenolic and flavonoid contents of *S. mahagoni* ethanolic extract (SME)

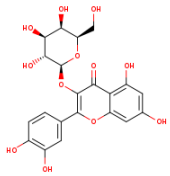
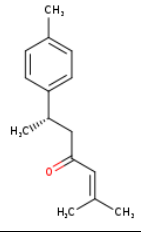
Sample	TFC (mgQE/g w.b)	TPC (mgGAE/g w.b)
SME1	453.38	298.72
SME2	435.66	283.02
SME3	487.69	317.95
Mean	458.91 ± 21.60	299.90 ± 14.28

3.3 Compound identification of *S. mahagoni* ethanolic extract using LC-HRSM analysis

The identification of active compound in *S. mahagoni* ethanolic extract was continued with LC-HRMS analysis. Around 40 compound was found in in *S. mahagoni* ethanolic extract. Three active compound was selected for future analysis, there are 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-{[(2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan--2-yl]oxy}-4H-chromen-4-one (Quercitrin), (+)-ar-Turmerone, Hyperoside, more information as shown in Table 3. Future analysis with these compounds including druglikeness analysis and molecular interactions prediction.

Table 3. Characteristics of active compound from *S. mahagoni* ethanolic extract

Name	Structure	Formula	Calc. MW	RT [min]	Area (Max.)	mzCloud Best Match
Hyperoside		C21 H20 O12	464.09	7.16	5.42E+07	99.3

Name	Structure	Formula	Calc. MW	RT [min]	Area (Max.)	mzCloud Best Match
Quercitrin		C21 H20 O11	448.10	7.84	2.18E+07	99.1
(+)-ar-Turmerone		C15 H20 O	216.15	17.48	1.60E+07	98.1

3.4 Drug likeness analysis based on Lipinsky's role and ADME analysis

A druglikeness analysis was conducted based on Lipinsky's role which supported with ADME analysis. Table 4 presents a drug-likeness analysis that is categorized into four parameters: molecular mass, hydrogen bond donors, hydrogen bond acceptors, and high lipophilicity. Overall, two of four criterias were effective in Quercitrin, (+)-ar-Turmerone, and Hyperoside. Additionally, pharmacokinetic information on the toxicity, excretion, metabolism, distribution, and absorption of hyperoside, quercitrin, and (+)-ar-Turmerone was assessed in relation to the ADME study (Table 5).

Table 4. Lispinsky's role of Quercitrin, (+)-ar-Turmerone, and Hyperoside

Lipinsky's role	Hyperoside	Quercitrin	(+)-ar-Turmerone
Molecular mass	464.38	448.10	216.32
High lipophilicity	0.54	0.49	4.02
Hydrogen bond donors	8	7	0
Hydrogen bond acceptors	12	11	1

Table 5. ADME prediction of Quercitrin, (+)-ar-Turmerone, and Hyperoside

Properties	Parameters		Ligands		
			Hyperoside	Quercitrin	(+)-ar-Turmerone
Absorption	Water Solubility (log mol/L)		-2.92	-2.90	-4.45
	Intestinal Absorption (%)		48.00	52.71	94.49
Distribution	Volume Distribution (VDss) (log L/Kg)		1.85	1.52	0.62
Metabolism	Inhibitor of	CYP1A2	-	-	-
		CYP2C19	-	-	-
		CYP2C9	-	-	-
		CYP2D6	-	-	-
		CYP3A4	-	-	-
Excretion	Total Clearance (mL/min/kg)		0.39	0.36	0.29

3.5 Molecular docking analysis

The docking results for MDM2 and AKT-1 with the three compounds found in *S. mahagoni* ethanolic extract—Quercitrin, (+)-ar-Turmerone, and Hyperoside showed binding affinities of −7.5, −6.9, and −7.3 kcal/mol for MDM2, respectively, compared to a known inhibitor, imidazole, which has a binding affinity of −9.6 kcal/mol. For AKT-1, Quercitrin, (+)-ar-Turmerone, and Hyperoside exhibited binding affinities of −7.8, −6.5, and −8.0 kcal/mol, respectively, in contrast to the known inhibitor AZD, which has a binding affinity of −9.1 kcal/mol. Furthermore, active compound from *S. mahagoni* exhibit comparable amino acid residue interactions to those of the control ligand (Table 6).

Table 6. Binding affinity and amino acid residue between compounds from *S. mahagoni* leave ethanolic extract and AKT-1 or MDM2

Ligand	AKT-1		MDM2	
	Binding Affinity	**Amino acid residue**	**Binding Affinity**	**Amino acid residue**
(+)-ar-Turmerone	-6.5	MET227 ; ALA177; VAL164; MET281; LEU156; LYS179	-7.3	ILE19; TYR100; HIS96; LEU54; GLY58; PHE86; LEU57; ILE61; VAL93; ILE99; PHE91
Quercitrin	-7.8	GLY162; LYS158; GLU234; MET281; VAL164; ALA177	-7.5	LEU54; VAL93; ILE61; ILE99; HIS96
Hyperoside	-8	PHE161; LYS158; VAL164; GLU278; GLY157	-6.9	PHE55; GLY58; LEU54; ILE61; ILE99; VAL93 ; GLN72
Imidazole			-9.6	HIS96; LEU54; ILE99; LEU57; PHE91; PHE86; ILE61; VAL93
AZD5363	-9.1	GLU278; GLU234; MET281; ALA230; ASN279; GLY157; MET227; LEU181; LYS179; VAL164; LEU156; ALA177; GLY162		

Note : Glu is glutamate; Met is methionine; Phe is phenylalanine; Ile is leucine; Ala is alanine; Lys is lysine; His is histidine; Leu is leucine; Asn is Asparagine; Val is valine; Gly is glycine; Gln is glutamine; and Try is tyrosine. Underline is mean comparable amino acid residue interactions to the control ligand.

Further evaluation of the compounds' orientation when interacting with the active sites of AKT-1 and MDM2 (Figures 1 and 2, respectively) is crucial for assessing their potential as inhibitors. The analysis indicated that these compounds from the *S. mahagoni* ethanolic extract bind to the active sites of AKT-1 and MDM2 similarly to the known inhibitors, suggesting that Quercitrin, (+)-ar-Turmerone, and Hyperoside could be promising candidates for inhibiting these proteins (Table 6).

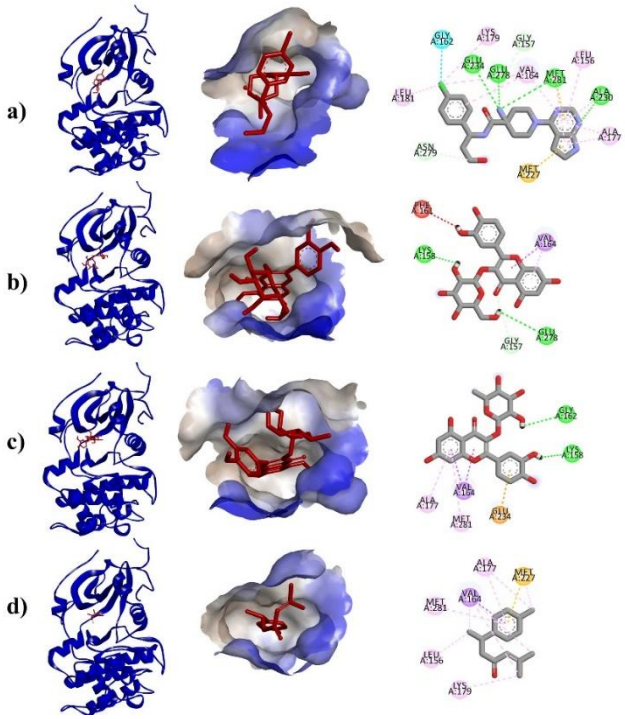


Figure 1. Interaction between AKT-1 and compounds from *S. mahagoni* leaves ethanolic extract. a) docking of AZD5363 as native ligand inhibitor; b) docking of hyperoside; c) docking of quercitrin; d) docking of (+)-ar-Turmerone. On the left, AKT-1 is presented in blue ribbon structure with ligands presented as red. In the middle, hydrophobicity surface map of the active site of AKT-1 with the ligands presented as red cylinders. At the right, cylinder representation 2D interaction between AKT-1 and ligands

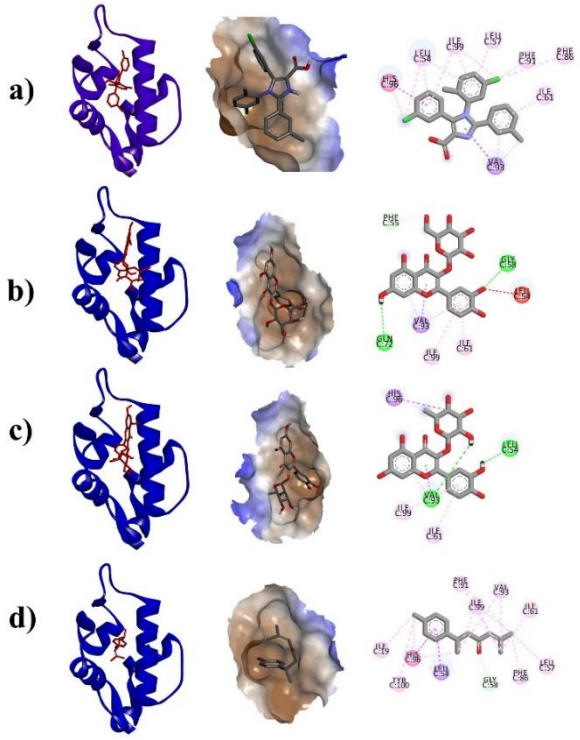


Figure 2. Interaction between MDM2 and compounds from *S. mahagoni* leaves ethanolic extract. a) docking of imidazole as native ligand inhibitor; b) docking of hyperoside; c) docking of quercitrin; d) docking of (+)-ar-Turmerone. On the left, MDM2 is presented in blue ribbon structure with ligands presented as red. In the middle, the hydrophobicity surface map of the active site of MDM2 with the ligands presented as red cylinders. At the right, cylinder representation 2D interaction between MDM2 and ligands

4. DISCUSSION

This study evaluated and predicted the active compound that is contained in *S. Mahagoni* ethanolic extract and their potency for inhibiting cancer cell growth. Phytochemicals are natural bioactive compounds found in plants, such as medicinal plants, which have work act as a defense system against diseases. They exhibit extensive potential as antioxidants, anticancer, anti-inflammatory, and immunomodulator in the body system. In this study, present that *S. Mahagoni* ethanolic extract has potency as antioxidant that have been proven their capability to inhibiting DPPH free radical. This study was supported by another research that another part of *S. Mahagoni* plant, such as seed and bark, also has been reported have potency to inhibiting DPPH free radical [17,20].

Furthermore, In the study revealed a presence of flavonoids and phenolic in the *S. Mahagoni* ethanolic extract, as TFC 458.91 ± 21.60 (mgQE/g w.b) and TPC 299.90 ± 14.28 (mgGAE/g w.b), respectively. The result of this study about TFC and TPC of *S. Mahagoni* leave ethanolic extract was supported by another study about *S. Mahagoni*. 24 compounds were characterized by the GC-MS, and were grouped into phenolics, fatty acids and hydrocarbons, and terpenoids [18] was found in *Mahagoni* leave methanolic extract. Another part of *S. Mahagoni* plant, such as seed and bark, also has been reported contain the phytochemicals [21–24].

Flavonoids and phenolics are classes of compounds commonly referred to as plant secondary metabolites. They are characterized by an aromatic ring with at least one hydroxyl group. Over 8,000 naturally occurring phenolic compounds derived from plants have been documented. Besides that, screening single compounds needs to be conducted to know the specific compound that is contained in this extract. Additionally, further screening showed that this extract contains several plant secondary metabolites, including Quercitrin, (+)-ar-Turmerone, and Hyperoside. These compounds have been reported to have several pharmaceutical function, such as antiinlamatory for quercitrin [25], anticancer for (+)-ar-Turmerone [26], and anti-cancer, brain-protective, neuroprotective, cardioprotective and renal-protective activities for hyperoside [27].

Chemicals intended for use as oral drugs must possess specific characteristics that align with the criteria for drug-likeness. There are two primary types of analyses used to evaluate drug-likeness: Lipinski's Rule and ADME prediction. Lipinski's Rule identifies key physicochemical properties common to drug-like compounds, while ADME prediction evaluates Absorption, Distribution, Metabolism, and Excretion, as well as Toxicity (ADME). This analysis provides insights into oral bioavailability, cellular permeability, metabolism, elimination, and toxicity, which are crucial for understanding a drug molecule's pharmacokinetics and pharmacodynamics. Bioactive compounds isolated from plants can be considered lead compounds if they exhibit a favorable ADME profile. Even if these compounds do not always meet standardized ADME criteria, modifications or substitutions with similar compounds or herbs may still achieve the desired therapeutic effects in herbal medicine.

In the absorption parameter, two critical factors are water solubility and intestinal absorption. Water solubility is essential for drug bioavailability. The ESOL model is commonly used to categorize solubility based on a logarithmic scale (Insoluble <-10, Poorly soluble <-6, Moderately soluble <-4, Soluble <-2, Very soluble <0) [15]. In this study, the water solubility of the three compounds falls within the Moderately soluble to Soluble range. (+)-ar-Turmerone shows a high intestinal absorption value of 94.489%, indicating excellent absorption, whereas Hyperoside and Quercitrin have lower intestinal absorption values of 47.999% and 52.709%, respectively. Optimal intestinal absorption is typically above 80% [28].

The prediction of a drug's or lead compound's distribution within the body is assessed by its volume of distribution, which typically ranges from 0.5 to 3 L/kg.

Quercitrin, (+)-ar-Turmerone, and Hyperoside exhibit relatively favorable drug delivery characteristics in the bloodstream. The metabolism of a drug involves evaluating whether it can inhibit CYP (Cytochrome P450) enzymes, which are crucial for the digestive system and Phase 1 metabolic processes. Quercitrin, (+)-ar-Turmerone, and Hyperoside do not inhibit these CYP enzymes. The final pharmacokinetic parameter to consider is the excretory system. Faster excretion rates lead to higher total clearance values, which generally benefit the body.

Drug-likeness analysis often follows Lipinski's Rule, which provides criteria for evaluating chemical and physical properties necessary for a compound to be considered a viable drug. Lipinski's Rule includes: Log P less than 5, fewer than 10 hydrogen bond acceptors, fewer than 10 hydrogen bond donors, and a molecular mass under 500 Dalton [29]. Compounds from *S. mahagoni* ethanolic extract typically have up to two violations of this rule. According to Lipinski's Rule, a compound is suitable for oral administration if it has no more than one violation. Compounds with two or more violations usually exhibit poor solubility and permeability [30].

This study also aimed to predict the potential of compounds from *S. mahagoni* leaves ethanolic extract in inhibiting cancer cell growth through molecular docking. The binding affinity of Quercitrin, (+)-ar-Turmerone, and Hyperoside with MDM2 and AKT-1 was evaluated. Both MDM2 and AKT-1 are targets in cancer therapy. MDM2 is involved in the degradation of p53, a pro-apoptotic protein , while AKT-1 is crucial for various cellular processes including growth, proliferation, survival, and angiogenesis [31,32]. The findings suggest that Quercitrin, (+)-ar-Turmerone, and Hyperoside may have potential as inhibitors of MDM2 or AKT-1. However, further study, especially in vitro study, should be conducted to validate the activity of the studied compounds.

CONCLUSION

The current study indicates that the ethanolic extract of *S. mahagoni* leaves possesses antioxidant properties, attributable to its content of various phenolic and flavonoid compounds, including Quercitrin, (+)-ar-Turmerone, and Hyperoside. These compounds not only meet Lipinski's criteria for drug-likeness but also show potential as inhibitors of MDM2 and AKT-1. Moreover, Quercitrin, (+)-ar-Turmerone, and Hyperoside might inhibit MDM2 and CXCR4, potentially inducing apoptosis in cancer cells. Further in vitro research is needed to validate these compounds' efficacy and confirm their potential therapeutic applications.

Conflict of Interest

Authors declare that there is no have potential conflict of interest

Funding

This research was funded by Faculty of Mathematics and Natural Science, Universitas Negeri Surabaya trough Research funding with number 32079/UN38.3/LK.04.00/2024

REFERENCES

1. Widodo N, Puspitarini S, Widyananda MH, Alamsyah A, Wicaksono ST, Masruri M, et al. Anticancer activity of Caesalpinia sappan by downregulating mitochondrial genes in A549 lung cancer cell line [version 2; peer review: 2 approved]. 2022.
2. George BP, Chandran R, Abrahamse H. Role of Phytochemicals in Cancer Chemoprevention: Insights. *Antioxidants*. 2021;10:1455.

3. Wargasetia TL, Permana S, Widodo N. Potential use of compounds from sea cucumbers as MDM2 and CXCR4 inhibitors to control cancer cell growth. *Exp Ther Med*. 2018;16:2985–91.
4. Osanloo M, Yousefpoor Y, Alipanah H, Ghanbariasad A, Jalilvand M, Amani A. In-vitro Assessment of Essential Oils as Anticancer Therapeutic Agents: A Systematic Literature Review. *Jordan Journal of Pharmaceutical Sciences*. 2022;15:173–203.
5. Widyananda MH, Wicaksono ST, Rahmawati K, Puspitarini S, Ulfa SM, Jatmiko YD, et al. A Potential Anticancer Mechanism of Finger Root (*Boesenbergia rotunda*) Extracts against a Breast Cancer Cell Line. *Scientifica*. 2022;2022:e9130252.
6. Wargasetia TL, Ratnawati H, Widodo N, Widyananda MH. Bioinformatics Study of Sea Cucumber Peptides as Antibreast Cancer Through Inhibiting the Activity of Overexpressed Protein (EGFR, PI3K, AKT1, and CDK4). *Cancer Inform*. 2021;20:11769351211031864.
7. Wargasetia TL, Widodo null. Mechanisms of cancer cell killing by sea cucumber-derived compounds. *Invest New Drugs*. 2017;35:820–6.
8. Fathima S, Durairaj SK, Padigaru M, Cma B. Efficacy of a Polyherbal Supplement in Enhancing Immune Cells in Individuals Frequently Susceptible to Cold and Flu. *Current Developments in Nutrition*. 2022;6:977.
9. Zaki PH, Gandaseca S, Rashidi NM, Ismail MH. Traditional usage of medicinal plants by Temiar tribes in the State of Kelantan, Peninsular Malaysia. *Forest and Society*. 2019;3:227–34.
10. Budiyanto M, Puspitarini S, Prasetyo S, Subekti H, Birhan YS, Qosyim A, et al. In vitro investigation on *Pennisetum purpureum* leaf extracts grown in Indonesia of phytochemical components, optical characteristics, and antioxidant-antibacterial activities. *Braz J Biol*. 2024;84:e280855.
11. Kuswanti N, Widyarti S, Widodo W, Rifa'i M. Apoptotic and necrotic lymphocytes after treatment of stem bark extract of Plumeria rubra L invitro. *IOP Conf Ser: Earth Environ Sci*. 2019;391:012031.
12. Ismail WH, Abusara OH, Ikhmais B, Abul-Futouh H, Sunoqrot S, Ibrahim AIM. Design, Synthesis, and Biological Activity of Coniferyl Aldehyde Derivatives as Potential Anticancer and Antioxidant Agents. *Jordan Journal of Pharmaceutical Sciences*. 2023;16:368–80.
13. Utaminingrum W, Nofrianti N, Hartanti D. Diversity and use of medicinal plants for traditional women's health care in Northern Banyumas, Indonesia. *Biodiversitas Journal of Biological Diversity* [Internet]. 2022 [cited 2024 Jan 24];23. Available from: https://smujo.id/biodiv/article/view/10300
14. Rahhal BM, Jaradat N, Issa L, Hussein F, Amara G, Gazawi L, et al. Unveiling the Phytochemical Profiling, hypolipidemic, hypoglycemic and antioxidant effects of different extracts from Lavandula stoechas L. (French lavender) grown in Palestine. *Jordan Journal of Pharmaceutical Sciences*. 2025;18:509–23.
15. Kamble ANS, Mitkar AA. Swiss ADME predictions of pharmacokinetics and drug-likeness properties of secondary metabolites present in Trigonella foenum-graecum. *J Pharmacogn Phytochem*. 2023;12:341–9.
16. Novian DR, Ikhwani AZN, Winarso A. Uji farmakodinamik, drug-likeness, farmakokinetik dan interaksi senyawa aktif kayu ular (Strychnos lucida) sebagai inhibitor Plasmodium falciparum secara in silico. *Jurnal Veteriner Nusantara*. 2019;2:70–8.
17. Pratiwi S, Emelda E, Kusumawardani N, Munir MA, Azizah A. Analysis of Total Phenolic Content and Antioxidant Activity of Mahogany Seed Infusion (Swietenia mahagoni (L.) Jacq.). *Jurnal Gizi dan Dietetik Indonesia (Indonesian Journal of Nutrition and Dietetics)* [Internet]. 2024 [cited 2024 Aug 14];12. Available from: https://ejournal.almaata.ac.id/index.php/IJND/article/view/3768

18. Masendra M, Purba BAV, Arisandi R, Lukmandaru G. Chemical investigation of methanol extracts of Swietenia mahagoni leaves and its antioxidant activity. *Wood Research Journal*. 2014;5:51–6.
19. Susilo B, Oktavianty O, Rahayu F, Handayani MLW, Rohim A. Potential transformation of seagrass (*Syringodium isoetifolium*) into a bioactive food ingredient using different extraction techniques [Internet]. *F1000Research*; 2023 [cited 2024 Aug 16]. Available from: https://f1000research.com/articles/12-1078
20. Turangan ATM, Wewengkang DS, Yudistira A. UJI AKTIVITAS ANTIOKSIDAN EKSTRAK ETANOL KULIT BATANG MAHONI (Swietenia mahagoni Jacq.) MENGGUNAKAN METODE DPPH (1,1 diphenyl-2-picrylhydrazyl). *PHARMACON*. 2019;8:548–55.
21. Borah A, Selvaraj S, Holla SR, De S. Extraction and characterization of total phenolic and flavonoid contents from bark of *Swietenia macrophylla* and their antimicrobial and antioxidant properties. *Arabian Journal of Chemistry*. 2022;15:104370.
22. Nathasa K, Hakim AR, Hidayah N. COMPARISON OF TOTAL FLAVONOID CONTENT BASED ON DIFFERENCES IN ETHANOL SOLUTION CONCENTRATION FROM MAHOGANY FRUIT SEEDS (Swietenia mahagoni). *International Conference on Health and Science*. 2021;1:190–202.
23. Hartati H, Salleh LM, Idris IS, Azis AA. WOUND HEALING PROPERTIES OF SWIETENIA MAHAGONI SEED EXTRACTED USING SCCO2: AN IN VITRO STUDY. *Jurnal Teknologi* [Internet]. 2018 [cited 2024 Jan 23];81. Available from: https://journals.utm.my/index.php/jurnalteknologi/article/view/12195
24. Sahgal G, Ramanathan S, Sasidharan S, Mordi M, Ismail S, Mansor S. In Vitro Antioxidant and Xanthine Oxidase Inhibitory Activities of Methanolic Swietenia mahagoni Seed Extracts. *Molecules (Basel, Switzerland)*. 2009;14:4476–85.
25. Comalada M, Camuesco D, Sierra S, Ballester I, Xaus J, Gálvez J, et al. In vivo quercitrin anti-inflammatory effect involves release of quercetin, which inhibits inflammation through down-regulation of the NF-κB pathway. *European Journal of Immunology*. 2005;35:584–92.
26. Cao W, Chen X, Xiao C, Lin D, Li Y, Luo S, et al. Arturmerone inhibits the proliferation and mobility of glioma by downregulating cathepsin B. *Aging*. 2023;15:9377–90.
27. Xu S, Chen S, Xia W, Sui H, Fu X. Hyperoside: A Review of Its Structure, Synthesis, Pharmacology, Pharmacokinetics and Toxicity. *Molecules*. 2022;27:3009.
28. Khan MF, Nahar N, Rashid RB, Chowdhury A, Rashid MA. Computational investigations of physicochemical, pharmacokinetic, toxicological properties and molecular docking of betulinic acid, a constituent of Corypha taliera (Roxb.) with Phospholipase A2 (PLA2). *BMC Complement Altern Med*. 2018;18:48.
29. Karami TK, Hailu S, Feng S, Graham R, Gukasyan HJ. Eyes on Lipinski's Rule of Five: A New "Rule of Thumb" for Physicochemical Design Space of Ophthalmic Drugs. *Journal of Ocular Pharmacology and Therapeutics*. 2022;38:43.
30. Benet LZ, Hosey CM, Ursu O, Oprea TI. BDDCS, the Rule of 5 and Drugability. *Adv Drug Deliv Rev*. 2016;101:89–98.
31. Chibaya L, Karim B, Zhang H, Jones SN. Mdm2 phosphorylation by Akt regulates the p53 response to oxidative stress to promote cell proliferation and tumorigenesis. *Proceedings of the National Academy of Sciences*. 2021;118:e2003193118.
32. Singh S, Ramamoorthy M, Vaughan C, Yeudall WA, Deb S, Palit Deb S. Human oncoprotein MDM2 activates the Akt signaling pathway through an interaction with the repressor element-1 silencing transcription factor conferring a survival advantage to cancer cells. *Cell Death Differ*. 2013;20:558–66.

سويتينيا ماهاغوني يترك المستخلص الإيثانولي: نشاط مضاد للأكسدة في المختبر، وتحديد المركب النشط والتنبؤ بالسيليكو كمثبط بروتين AKT−1 وMDM2

سابتي بوسبيتاريني* [1]، محمد بوديانتو [1]، محمد عارف مهديانور [1]، رويهانا وليول مرسييداه [1]، إرتيكا فيتري ليسنانتي [2]، فصيح بنتانج إلهامي [1]

[1]برنامج دراسة تعليم العلوم، كلية الرياضيات والعلوم الطبيعية، جامعة نيجيري سورابايا، سورابايا، إندونيسيا

[2]برنامج دراسة التربية الحيوانية، كلية الزراعة، جامعة قادري الإسلامية، كديري، إندونيسيا

ملخص

يدعم الارتباط الوثيق بين الممارسات التقليدية والخصائص الدوائية لهذه النباتات استمرار استخدامها في علاج مختلف الحالات الصحية .قيّمت هذه الدراسة وتوقعت المركب النشط في المستخلص الإيثانولي لأوراق سويتينيا ماهاغوني وفعاليته في تثبيط نمو الخلايا السرطانية .شمل التحليل قياس تثبيط الجذور الحرة DPPH، ومحتوى الفينول والفلافونويد الكلي، وتقييم تشابه الأدوية، ودراسات الالتحام الجزيئي .تشير النتائج إلى أن المستخلص الإيثانولي لأوراق S. mahagoni يُظهر خصائص مضادة للأكسدة نظرًا لاحتوائه على مركبات فينولية وفلافونويدية مثل الكيرسيترين، و(+)-ar-Turmerone، وهايبروسيد، والتي تُلبي أيضًا معايير ليبينسكي .بالإضافة إلى ذلك، قد تعمل هذه المركبات كمثبطات لـ MDM2أو AKT-1، مما قد يُعيق MDM2وAKT-1 ويُحفز موت الخلايا المبرمج في الخلايا السرطانية .ينبغي إجراء المزيد من الأبحاث في المختبر للتحقق من فعالية المركبات المدروسة.

الكلمات الدالة: مضاد للسرطان، Insilico، دواء نباتي، مستقلب ثانوي، Swietenia mahagoni.

* ***المؤلف المراسل: سابتي بوسبيتاريني***

saptipuspitarini@unesa.ac.id

تاريخ استلام البحث 2024/08/16 وتاريخ قبوله للنشر 2024/09/21.