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FULL PAPER

In silico assessment of anti-biofilm properties of bioactive compounds from *Parameria laevigata* (Juss.) Moldenke identified by UPLC QToF MS/MS

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Parameria laevigata (Juss.) Moldenke is a plant with the potential to act as an antifungal agent against various diseases, including vaginitis. This is primarily due to quinones, flavonoids, saponins, triterpenoids, tannins, alkaloids, polyphenols, and steroids in the bark. Vaginitis is a condition caused by *Candida albicans* fungal through biofilm formation. The attachment of the fungal to epithelial cells and subsequent invasion of host cells often require the presence of Als3p, which can also serve as a receptor *in silico*. Therefore, this study aims to determine compounds of *P. laevigata* that are associated with Als3p and possess anti-biofilm properties *in silico*. The ultrasound-assisted Extraction (UAE) method was used for extraction, while the UPLC-QToF-MS/MS instrument was used to determine the metabolite profile. MOE software determined molecular docking between Als3p (PDB id: 4LEE) and metabolite profiling. MassLynx software was used for the data interpretation, and confirmation was performed on various websites, including MassBank, NIST, PUB-CHEM, HMDB, MoNA, and DrugBank. The results showed that *P. laevigata* stem bark ethanol extract contained 19 known compounds. In addition, 3 compounds were found to possess antimicrobial activity, including myristicin, valyl phenylalanine, and oleanane. *In silico* investigation revealed that myristicin, valyl phenylalanine, and oleanane could inhibitAls3p receptor. Based on the results, *P. laevigata* stem bark ethanol extract contained valyl phenylalanine, myristicin, and oleanane, indicating anti-biofilm activity. Myristicin, valyl phenylalanine, and oleanane were also shown to have the ability to inhibit the Als3p receptor.

KEYWORDS

Als3p; anti-biofilm; medicine; metabolite profile; *Parameria laevigata*; UPLC-QToF-MS/MS.

Introduction

Parameria laevigata (Juss.) Moldenke is a member of the Apocynaceae plant family, which typically grows wild in forests and other well-lit areas with fertile soil. In addition, several studies showed that the bark contains flavonoids, quinones, saponins, tannins, triterpenoids, steroids, alkaloids, and polyphenols [1,3]. *P. laevigata* is often widely used as a weight loss or slimming agent and medicine for wounds, scabs, dysentery, uterine pain after maternity, analgesic, and antibacterial [2,5]. Various communities also

use water infusion from *P. laevigata* stem bark as empirical therapy to treat vaginal disorder or vaginitis.

According to previous studies, vaginitis is caused by *Candida albicans,* a fungal that can form biofilm formation. Several reports showed that microbes with the ability to produce biofilm formation typically had greater resistance to antimicrobial agents than individual cells. In addition, fungal infections caused by biofilms often pose challenges in treatment, requiring approximately 1000 times the antifungal dose to achieve comparable outcomes in planktonic cells [6]. Antimicrobial agents have been reported to be generally more effective against viable cells. Consequently, antimicrobial agents against planktonic cells are ineffective against biofilm cells [7]. Therefore, it is imperative to create alternatives to combat biofilm formation due to infection by the pathogen *C. albicans* using plants.

In line with previous studies, biofilm is a collection of microorganism cells that adhere to a surface and produce Extracellular Polysaccharide Substances (EPS), which contain polysaccharides, proteins, and DNA [8]. According to Crouzet, biofilm formation stages consist of microbial attachment to a surface, biofilm maturation, microcolony formation, and release (dispersal) [9]. Als3p, a protein belonging to the agglutinin-like sequence group, is crucial in facilitating the attachment stage, an important phase in forming biofilms from *C. albicans* [10,13]. Blocking of Als3p or preventing ALS3 gene expression can significantly reduce adhesion to epithelial cells [14]. A previous report also showed the use of Als3p as an *in silico* receptor.

Research on the phytochemical content of plants is still being carried out to determine the active natural compounds of medicines. Indonesia, located in South-East Asia, boasts a remarkable biodiversity of medicinal plants and diverse ethnic groups [27]. Various types of flavonoid compounds in the form of pure compounds, such as quercetin, kaempferol, luetiolin, and others, have been widely isolated from this plant [28]. Therefore, this study aims to determine compounds of *P. laevigata* that are associated with Als3p and possess anti-biofilm properties *in silico*. Until now, there has been no research on *in silico* studies using *P. laevigata*. The urgency of this research is to determine the antibiofilm activity of *P. laevigata* at the attachment stage so that it can be used as an alternative therapy to reduce the incidence of resistance due to antimicrobial use.

Experimental

Materials

The materials utilized in this study comprised *P. laevigata* (Juss.) Moldenke stem bark (PLSB) from CV. Merapi Farma Herbal Yogyakarta, Ethanol p.a (Merck), acetonitrile p.a (Merck), ammonium formate p.a (Merck), methanol p.a (Merck), and formic acid p.a (Merck).

Extraction of parameria laevigata (juss.) moldenke

The dried powder (500 grams) of PLSB was extracted with 5 L of 70% and 96% ethanol using the Ultrasound-Assisted Extraction (UAE) method for 10 min, and the extraction process was repeated three times. The filtrates were then concentrated using a rotary evaporator and dried in an oven to obtain 70% *P. laevigata* stem bark ethanol extract (PLE-70) and 96% *P. laevigata* stem bark ethanol extract (PLE-96).

Metabolite profiling by UPLC-QTOF-MS/MS

Metabolite profiling, employing UPLC-QToF-MS/MS equipment, was carried out at the Forensic Laboratory Center of the Indonesian National Police Criminal Investigation Agency. Furthermore, extracts were acquired utilizing

the SPE (Solid Phase Extraction) technique. As much as 5 µL of each sample was injected into an MS Xevo G2-S QToF detector-equipped ACQUITY UPLC® H-Class System (Waters, USA). The samples were separated on an ACQUITY BEH C18 column (1.7 m; 2.1 50 mm) utilizing acetonitrile with 0.1% formic acid and water with 0.1% formic acid as the mobile phase at a 0.2 mL/min flow rate. Chromatogram data and m/z spectra for each observed peak were also extracted from the UPLC-QToF-MS/MS analysis results employing MassLynx 4.1 software.

Identification compounds of parameria laevigata stem bark ethanol extract

MassLynx software was employed to examine the chromatogram data to determine chemical compound components and create molecular formulas. The information was confirmed on the ChemSpider website (www.chemspider.com). The MassBank, NIST, PUB-CHEM, HMDB, MoNA, and DrugBank websites were used, and the previously discovered chemical formula was entered to find the IUPAC/ACD name. In addition, the spectra values matched the MassBank, NIST, PUB-CHEM, HMDB, MoNA, and DrugBank databases.

Als3p protein target download and preparation

Docking studies were conducted on the active site of the Als3p receptor (PDB code: 4LEE). The receptor's molecular structure was sourced from the RCSB Protein Data Bank (PDB) (https://www.rcsb.org/). Moreover, the Als3p receptor was prepared using MOE 2022. The Als3p protein, identified by the code 4LEE, comprised 4 chains labeled as A, B, C, and D. Nevertheless, only Chain A was employed in the docking process.

Preparation of metabolite profile compound

Myristicin, valyl phenylalanine, and oleanane structures were initially depicted using the ChemDraw 20.0 software before being transferred to Chem3D 20.0. Energy minimization was conducted utilizing the MMFF94 method, and the resulting data was saved in both mol2 [SYBYL2 (.mol2)] and smi [SMILES (.smi)] formats. The ligand, formatted in mol2, was accessed using the AutoDockTools-1.5.6 program, where hydrogen atoms were eliminated (edit hydrogen-merge nonpolar), Gasteiger charges were applied, and it was subsequently saved in the *.pdbqt format.

Molecular docking

MOE was utilized for molecular docking, focusing on the site identified through MOE software 2022. The location of the ligand's pocket was concentrated on the region of amino acids responsible for creating interactions with the ligand.

Data analysis

Data analysis is used descriptively.

Results

Extraction of the stem bark of parameria laevigata

The sample used *Parameria laevigata* (Juss). The yield value of PLSB showed 9.86% for PLE-70 and 6.69% for PLE-96.

Identification of compounds of *Parameria laevigata* stem bark ethanol extract

The results obtained from the UPLC-QToF MS/MS instrument were in the form of a chromatogram. The compounds that appear early on the peak chromatogram are polar compounds, and their polarity decreases at the *peak* next. At this stage, repetition is carried out until a constant peak chromatogram is obtained. The chromatogram obtained was processed using the application *Masslynx* version 4.1 so that

the m/z spectra of each can be displayed at peak level on the chromatogram. Each chromatogram peak indicates one compound's presence [29,30]. The results are presented in (Table 1) and (Figures 1 and 2).

TABLE 1 Prediction compounds of PLE-70 and PLE-96

No.	RT (min)	PLE-70 % Area	PLE-70 Measured Mass (m/z)	PLE-96 % Area	PLE-96 Measured Mass (m/z)	Calculated Mass	Molecular Formula	Proposed Metabolite
1.	3.278	0.2461	156.0426	0.3325	156.0419	156.0423	$C_7H_8O_4$	Dimethyl itaconate
2.	4.199	0.7151	264.1476	-	-	264.1474	$C_{14}H_{20}N_2O_3$	Valyl-phenylalanine
3.	4.621	0.4036	208.0375	0.5203	208.0372	208.0372	$C_{10}H_8O_5$	Fraxetin
4.	5.274	3.7262	248.1049	2.8967	248.1049	248.1049	$C_{14}H_{16}O_4$	Prenyl caffeate
5.	5.831	1.0021	222.0525	1.2134	222.0524	222.0528	$C_{11}H_{10}O_5$	Fraxidin
6.	6.555	3.1588	206.0578	4.4052	206.0578	206.0579	$C_{11}H_{10}O_4$	Scoparone
7.	6.814	0.3548	192.0785	0.4476	192.0787	192.0787	$C_{11}H_{12}O_3$	Myristicin
8.	8.881	6.0723	344.1984	3.8202	344.1990	344.1988	$C_{21}H_{28}O_4$	11-Dehydro corticosterone
9.	9.120	0.8569	326.1879	-	-	326.1882	$C_{21}H_{26}O_3$	Octabenzone
10.	9.647	1.6929	402.1941	1.5268	402.1941	402.1944	$C_{25}H_{26}N_2O_3$	Aurantiamide
11.	10.267	0.9711	292.2044	0.8936	292.2035	292.2039	$C_{18}H_{28}O_3$	12-Oxo phytodienoic acid
12.	10.484	1.0580	452.3291	0.6579	452.3291	452.3291	$C_{30}H_{44}O_3$	Boldenone undecylenate
13.	10.794	3.6148	444.2054	3.5599	444.2054	444.2049	$C_{27}H_{28}N_2O_4$	Aurantiamide acetate
14.	11.032	0.6972	290.1879	0.2415	290.1870	290.1882	$C_{18}H_{26}O_3$	Octyl-methoxycinnamate
15.	11.166	0.4758	229.2409	0.3694	229.2409	229.2406	$C_{14}H_{31}NO$	Lauryl dimethylamine oxide
16.	11.539	1.7079	315.2774	1.2707	315.2772	315.2774	$C_{18}H_{37}NO_3$	4-Hydroxy-8-sphingenine
17.	12.903	2.3471	294.2194	1.9290	294.2194	294.2195	$C_{18}H_{30}O_3$	13-Oxo octadecadienoic acid
18.	13.058	3.107	276.2092	2.4350	276.2091	276.2090	$C_{18}H_{28}O_2$	Phenyl laurate
19.	13.409	0.0979	428.2927	0.1548	428.2927	428.2927	$C_{27}H_{40}O_4$	Hydroxy progesterone caproate
20.	16.699	-	-	0.1671	440.3654	440.3655	$C_{30}H_{48}O_2$	Oleanane
21.	17.753	-	-	0.9178	410.3548	410.3549	$C_{29}H_{46}O$	Stigmasta-3,5-dien-7-one

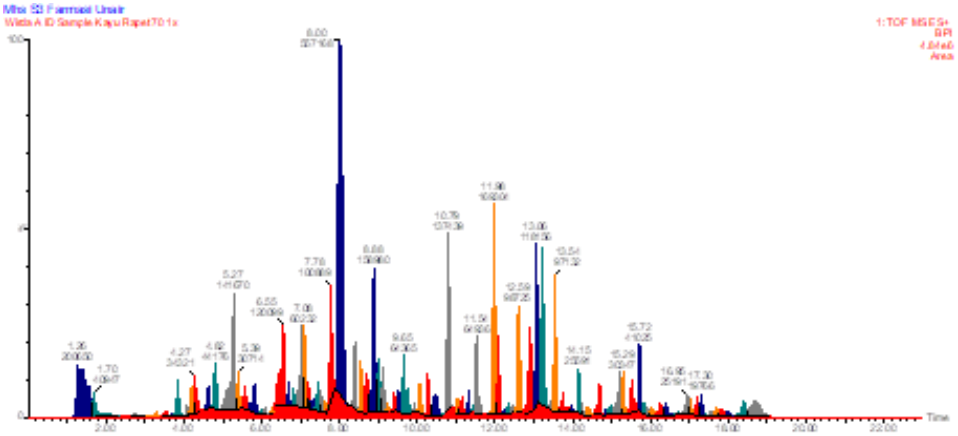

FIGURE 1 Total ion chromatogram (TIC) of PLE-70

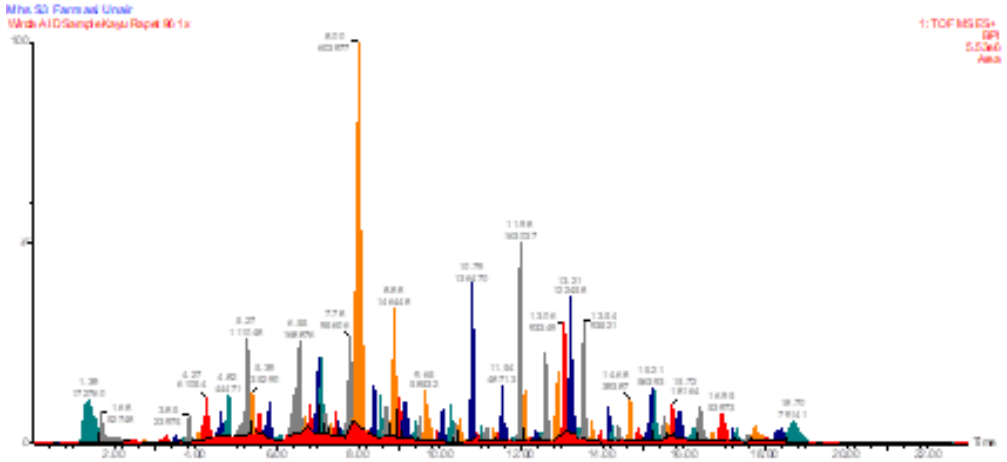

FIGURE 2 Total ion chromatogram (TIC) of PLE-96

Table 1 indicates all the compounds characterized in PLE-70 and PLE-96, such as % area, retention times, measured mass (m/z), molecular formula, calculated mass, and proposed metabolite. The PLE-70 chromatogram profile revealed 84 peaks, but only 19 compounds could be identified, while the PLE-96 chromatogram profile revealed 78 peaks, and 19 compounds could be identified. Table 1 provides 18 compounds from PLE-70 that were the same as PLE-96. The results showed that PLE-70 did not contain the oleanane and Stigmasta-3,5-dien-7-one contained in PLE-96. Meanwhile, PLE-96 did not contain the valyl phenylalanine and octabenzone content of PLE-70. Compounds in PLE-70 with antimicrobial activity included valyl-phenylalanine and myristicin., while antimicrobial compounds in PLE-96 were myristicin and oleanane.

Molecular docking simulation

Molecular docking was conducted with MOE, emphasizing the docking site determined through MOE software utilizing the ''Compute-Site Finder'' command and selected dummy atoms. The compounds were subsequently analyzed for receptor interaction through molecular docking. The parameter under observation was the affinity energy between ligands and receptors, evaluated by assessing the scoring bond energy and compound conformation at the binding site, representing the mode of interaction between two molecules, including electrostatic, hydrophobic, and hydrogen bond interactions. In addition, the docking results are presented in (Table 2), and the bonds of amino acids are demonstrated in (Figure 3).

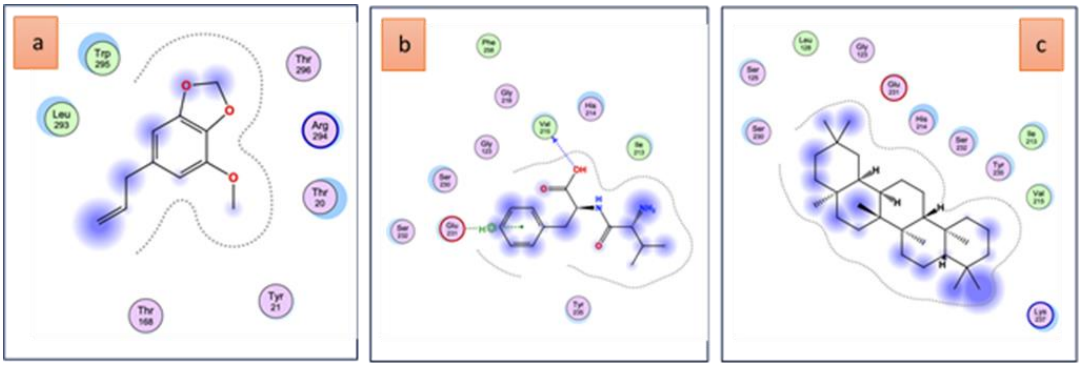

FIGURE 3 Interaction of myristicin (a), valyl phenylalanine (b), and oleanane (c) on amino acid residues of the 4LEE receptor

TABLE 2 The docking results of test ligands at the binding site of the 4LEE receptor

Parameters	Myristicin	Valyl Phenylalanine	Oleanane
△G (Kcal/mol)	-4.75	-4.69	-5.14
SD	0.21	0.13	0.10
Amino acid residues	Trp-295	-	-
	Leu-293	-	-
	Thr-296	-	-
	Arg-294	-	-
	Thr-20	-	-
	Tyr-21	-	-
	Thr-168	-	-
	-	Phe-258	-
	-	Gly-216	-
	-	Val-215	Val-215
	-	His-214	His-214
	-	Ile-213	Ile-213
	-	Gly-123	Gly-123
	-	Ser-230	Ser-230
	-	Ser-232	Ser-232
	-	Glu-231[a]	Glu-231
	-	Tyr-235	Tyr-235
	-	-	Ser-125
	-	-	Leu-128
	-	-	Lys-237

Description: a: H-bond.

Discussion

Candida albicans were the most common fungal species that caused health problems among all *Candida* species. In addition, Vulvovaginal Candidiasis (VVC) was the second most common disease among all vaginal infections [15]. In cases of severe hyperglycemia, fungal vaginitis was the most disturbing of the illnesses because it caused vaginal inflammation or infection. The yeast (fungal) organism, typically *Candida*, was the most frequent etiological agent for this infection. Given the significant and widespread levels of antibiotic resistance among fungal pathogenic, the search for antifungal drugs made from natural substances has become a priority. Consequently, there is an increasing global need for reports exploring natural plant-derived remedies effective against microbial pathogens [16]. This study emphasized using *P. laevigata*, which was widely accessible and affordable. The extraction process was performed using ethanol to extract all the contained compounds. In PLE-70 and PLE-96, only 19 peaks could be determined, with the remaining compounds being unknown. These unknown compounds might be identified either as impurities, still detectable by the instrument or as new compounds absent from the ChemSpider database, particularly those with high concentrations.

The receptor *in silico* study was Als3p with the PDB code, namely 4LEE. The critical molecule in *C. albicans* biofilm formation was a member of the Agglutinin-like sequence (Als) protein family, GPI-linked to β-1-6 glucans in the fungal cell wall [12]. This protein family included 8 members, namely Als1p to Als7p and Als9p, with varying degrees of structural and functional similarity [11]. Als1p, Als3p, and Als5p were protein adhesins that could mediate attachment to oral epithelial cells, endothelial cells, fibronectin, gelatine, fibrinogen, laminin, salivary pellicle, and type IV collagen [17]. Als1p was responsible for the initial attachment step of yeast cells to the surface, and Als3p was mainly responsible for transforming yeast cells into hyphal cells in the initiation and maturation phases [18].

Als3p was critical in attaching *C. albicans* hyphae to epithelial cells and subsequent invasion of host cells. ALS gene expression differed according to fungal morphology and location. The genes ALS1, ALS2, ALS3, and ALS9 showed frequent expression in clinical specimens of vaginal fluid. The ALS3 gene exhibited upregulation during infection in both vaginal and oral epithelial cells [19]. The epithelial internalization of *C. albicans* hyphae was facilitated by the invasive proteins Als3p and Ssa1p, which engaged with the E-cadherin receptor on vaginal epithelial cells and a hetero-dynamic receptor complex comprising Her2 (EGFR/Her2) and Epidermal Growth Factor Receptor (EGFR) [14].

Protein-ligand binding exclusively transpired when the free energy change exhibited a negative value. The bond's free energy is directly correlated with the stability of the protein-ligand interaction. Hence, protein ligands exhibited a low binding affinity energy within the system [20,22]. The bond's binding affinity energy reflected the ligand-protein complex's stability, a crucial attribute for assessing drug efficacy [23]. The binding energy was close to myristicin, valyl phenylalanine, and oleanane were -4.75 kcal/mol, -4.69 kcal/mol, and -5.14 kcal/mol, respectively.

(Figure 3) shows amino acids that were bound together in this study. In addition, there were similarities between amino acids bound to valyl phenylalanine and oleanane, namely Val-215, His-214, Ile-213, Gly-123, Ser-230, Ser-232, Glu-231, and Tyr-235. In the valyl phenylalanine compound, there was a hydrogen bond at Glu-231. Meanwhile, the difference in amino acids bound to the 2 compounds was Phe-258 and Gly-216, which were only found in valyl phenylalanine. Amino acids Ser-125, Leu-128, and Lys-237 were only found in the oleanane compound. Amino acids bound to the myristicin compound included Trp-295, Leu-293, Thr-296, Arg-294, Thr-20, Tyr-21, and Thr-168.

Apart from bond energy, it was crucial to account for various molecular interactions—including hydrogen, electrostatic, and hydrophobic bond interactions—when analyzing crucial amino acid residues interacting with docking ligands in conformation [24]. A hydrogen bond was established between H and O atoms of valyl phenylalanine. In the biological system (protein/receptor), the proton carrier pair, often called the hydrogen bond donor, typically consists of OH or NH_3 groups. The bond attained remarkable strength as the hydrogen atoms of the donor group were attached to highly electronegative atoms, causing the electron density of hydrogen atoms to shift toward neighboring atoms [25]. Hydrogen bonds further contributed to protein stability, albeit somewhat less than hydrophobic bonds [26].

Conclusion

In sum, *P. laevigata* stem bark ethanol extract contained valyl phenylalanine, myristicin, and oleanane. In addition, the presence of these compounds could prove that *P. laevigata* had anti-biofilm activity. The results also showed that myristicin, valyl phenylalanine, and oleanane could inhibit the Als3p receptor. Therefore, further research should continue with *in vitro* research.

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Authors' Contributions

Concept: W.A., D.J.P., I.K., and I.; Design: W.A., D.J.P., I.K., and I.; Supervision: D.J.P. and I.K..;

Resources: W.A.; Materials: W.A.; Data Collection and/or Processing: W.A.; Analysis and/or Interpretation: W.A., D.J.P., I.K., and I.; Literature Search: W.A., D.J.P., I.K., and I.; Writing: W.A.; Critical Reviews: D.J.P., I.K., and I.

Conflict of Interest

No potential conflict of interest was reported by the authors in this study.

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