Short Communication:

Chemical Profiling Ethyl Acetate Extract of *Basilicum polystachyon* Leaves and Exploration of Anticancer SIRT1 Inhibitors Using *In Silico* Approach

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Received: May 30, 2024
Accepted: November 5, 2024

DOI: 10.22146/ijc.96606

Abstract: *Cancer significantly increases prevalence and mortality rate making it a serious health concern currently, including breast cancer. The development of new drugs is a major effort to solve the cancer problems. Natural products are the primary source of medicinal compounds believed to have lower toxicity and side effects than synthetic drugs. This research aimed to reveal the chemical profile of the ethyl acetate extract of* Basilicum polystachyon *leaves. Through an* in silico *approach, this research studied the anticancer mechanism against the sirtuin1 (SIRT1) at the molecular level. Molecular docking simulations were performed to understand the interaction behavior of potential compounds as SIRT1 inhibitors. Based on these results, 117 individual compounds were successfully identified in the ethyl acetate extract. Molecular docking simulation revealed that ten compounds could inhibit SIRT1 better than the control inhibitor, indicating that these compounds have potential as anticancer agents. The prediction of these compounds' physicochemical properties and pharmacokinetics showed promising results and fulfilled the medicinal compound's criteria. These findings can be the basis for the application of phytochemical compounds as anticancer drugs, specifically potential compounds in* B. polystachyon *leaves.*

Keywords: *anticancer; SIRT1 inhibitor; molecular docking;* Basilicum polystachyon

■ INTRODUCTION

Cancer is currently a major health problem, and it is still unclear what causes cancer specifically, although many hypotheses have been reported. Cancer is categorized as a multifactorial disease caused by various environmental factors, such as pollution, chemicals, and carcinogenic substances [1]. Globally, cancer is the leading cause of death, and its incidence and prevalence continue to increase significantly [2]. Epidemiologist data from the Global Cancer Statistics (GLOBOCAN) in 2020 estimated approximately 19.3 million new cancer cases worldwide. Quantitatively, it is projected that the prevalence of cancer will continue to increase until it reaches 28.4 million by 2040, representing an increase of 47%. Among these cases, particularly in women, breast cancer contributed to 11.7% of all cancer cases and 6.9% of mortality globally in 2020 [3]. Handling this type of cancer with clinical treatment is a significant concern in the pharmaceutical world.

The discovery of more effective novel cancer drugs is currently a significant concern for resolving the high mortality caused by cancer and its prevalence. One of the target proteins of these drugs is known as sirtuin1 (SIRT1). SIRT1 has been linked to multiple biological processes, such as inflammation, aging, and metabolism, as it modulates these pathways [4]. SIRT1 is an isoform of the sirtuin enzyme bunch (SIRT1–SIRT7) that indicates cancer growth [5]. Overexpression of SIRT1 promotes the development of cancer cells in breast cancer because this enzyme promotes cancer cell survival, proliferation, and invasion.

Additionally, this enzyme plays a role in the acetylation of p53 protein and other critical oncogenes and tumor suppressors, including FOXO and NF-kB [6].

On the other cancer pathways, SIRT1 has been contributed to critical signaling cancer, such as the PI3K/Akt and mTOR pathways [4,7]. Discovering effective small-molecule inhibitors that specifically impact SIRT1 expression is becoming increasingly important due to SIRT1's crucial role.

Studies on the inhibition of the SIRT1 receptor with natural products were reported by several previous research using computational studies [8-10]. One of them was an alkaloid from *Psychotria* that was known to inhibit SIRT1 through interaction with the catalytic pocket [11]. Moreover, a 3,4,3′-tri-*O*-methylellagic acid compound isolated from *Syzygium polycephalum* bark showed good inhibitory activity in molecular docking studies with grid score lower than inhibitor control [7]. This proves that natural compounds have anticancer properties with lower toxicity and fewer side effects than synthetic drugs. One potential natural product that has never been reported for its anticancer activity is *Basilicum polystachyon*. To discover new anticancer drug compounds, the content of compounds in this plant needs to be revealed to test its activity using an *in silico* approach. The combination and integration of chemical profiling and molecular docking simulation is the primary focus of this study to explore the potential of *B. polystachyon* compounds in the ethyl acetate extract as anticancer agents' mechanism inhibitors of the SIRT1 enzyme. By considering the crucial parameters presented in this research, a structure-based approach is expected to contribute to recognizing the mechanism of action of the *B. polystachyon* compounds against the SIRT1 enzyme at the molecular level.

■ EXPERIMENTAL SECTION

Materials

The leaves of *B. polystachyon* (local name: sangket) were collected from Tuban, East Java, Indonesia. The chemicals used were ethyl acetate (Merck, Germany), Whatman paper 40, and distilled water.

Instrumentation

The equipment employed for this research involved a volumetric flask (Pyrex, USA), beaker glass (Pyrex, USA), extraction chamber, spatula, Whatman filter paper, Buchner funnel (Haldenwanger, Germany), vacuum pump (VE2100N, Value, Poland), vacuum rotary evaporator (R-300, Buchi, Switzerland), and Shimadzu LC-MS instrument (8040 Type, Shimadzu, Japan) for identification phytochemical compounds in the extract.

The molecular docking approach was performed using Toshiba Windows 10 64-bit operating system, Intel® Dual Core™ @2.16 GHz, and 4 GB RAM. The software used involved BIOVIA Discovery Studio Visualizer 2021 (Dassault Systèmes Biovia Corp., Vélizy-Villacoublay, France), AutoDock4.2 package (The Scripps Research Institute, La Jolla, CA, USA), and MarvinSketch (ChemAxon, Budapest, Hungary).

Procedure

Extraction of B. polystachyon *leaves*

The prepared samples consisted of *B. polystachyon* leaves. The extraction process was conducted using ethyl acetate solvent. After maceration at room temperature for 3 × 24 h, filtration was carried out with a vacuum pump and Whatman filter paper. The filtrate was concentrated using a vacuum rotary evaporator to remove solvent from the extract. The purified extracts were stored at 4 °C until further analysis.

Identification of secondary metabolites contained in the extract

The secondary metabolites present in the ethyl acetate extract of *B. polystachyon* leaves were detected using an LC-MS instrument (Shimadzu 8040 Type) completed with a Shimadzu Pack FC-ODS capillary column (2 × 150 mm id, 3 μm particle size) with a 1 μL injection volume and 80 min running time. The analysis instrument complemented with an electrospray ionization (ESI) source with the following parameters: column temperature 35 °C; capillary voltage 3.0 kV; flow rate 0.5 mL/min; ethyl acetate solvent; MS focused ion mode type $[M]^+$ in the *m/z* 50–1000 range; and mobile phase isocratic mode. The profile of secondary metabolites in the extract were discovered using NIST database libraries based on the chromatogram's molecular mass spectra and retention time compounds.

Molecular docking simulation

The 3D crystalline structure of the SIRT1 enzyme from *Homo sapiens* was retrieved from the Protein Data Bank (https://www.rcsb.org/). Water molecules and native ligands were sterilized from the protein receptor. The SIRT1 receptors were subsequently prepared with AutoDock by adding hydrogen atoms and Kollman charges [12]. Molecular docking was performed on the identified compound from the LC/MS results as ligand small molecules. The 3D conformers of the ligands were retrieved from the PubChem (https://pubchem.ncbi.nlm.nih.gov/) and then optimized this geometry through the use of Merck molecular force field (MMFF94) from the conformers tool, which is available in the MarvinSketch program [13].

Molecular docking simulations were conducted using AutoDock4.2 software on the active site of the SIRT1 receptor based on native ligand position, with a grid center of x = 42.205, y = −20.944, and z = 18.508, grid dimensions of 60 × 60 × 60 Å, and spacing of 0.375 Å. The Lamarckian genetic algorithm run of 100 was operated to find the optimum ligand conformation with the best docking score and binding position. The small molecule (6*S*)-2-chloro-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indole-6-carboxamide (4I5) in complex with receptor as a native ligand was used as a control inhibitor of the SIRT1 enzyme [14]. The docking procedure was validated by re-docking the native ligand on the receptor active site with an RMSD value ≤ 2 Å from the superimposition conformer [15-16]. After the process, molecular docking was simulated, and compounds with binding energy values less than those of the control inhibitor were selected as potential anticancer agents with the mechanism of action of SIRT1 inhibitors. The docking results of the optimal conformation were exported and analyzed using BIOVIA Discovery Studio Visualizer 2021 to visualize ligand-receptor interaction patterns and determine the residues of amino acids that play a role in the binding complex.

Drug criterion prediction

Drug criterion prediction of potential compounds from molecular docking results was analyzed using the SwissADME web server (http://www.swissadme.ch/index.php) [17]. This study included physicochemical properties, drug-likeness, bioavailability, and pharmacokinetics. All calculations were performed using the SMILES structures of the compounds.

■ RESULTS AND DISCUSSION

Identification of Secondary Metabolites Contained in the Ethyl Acetate Extract

The secondary metabolites contained in the ethyl acetate extract of *B. polystachyon* leaves are identified using LC-MS. The LC-MS chromatogram is displayed in Fig. 1. From these results, it can be recognized that there are 117 compounds contained in the ethyl acetate extract. As known that ethyl acetate is a semi-polar solvent can be able to extract polar and non-polar compounds contained in plant leaves, such as phenolics, flavonoids, glycosides, steroids, terpenoids, phenylpropanoids, polyketides, coumarins, and lignans. Phenolic acids and glycosides are examples of polar phenolic compounds that are frequently extracted using ethyl acetate. The phenolic compounds dominate the extract composition, which considers the presence of hydroxyl groups that are easily extracted with semi-polar solvents via hydrogen bonds [18]. The major compounds in the extract identified with high percent peak area are (1) quercetin-3-glucoside (2.71%); (2) quercetin-3-*O*-malonylglucoside (2.56%); (3) apigenin-7-*O*-rutinoside (2.72%); (4) 7-(((2*S*,3*R*,4*S*,5*S*,6*R*)-4,5-dihydroxy-6-(hydroxymethyl)-3-(((2*S*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)tetrahydro-2*H*-pyran-2-yl)oxy)-5-hydroxy-2-(4-hydroxyphenyl)-4*H*-chromen-4-one (3.00%); (5) naringin (2.53%); and (6) luteolin-7-glucuronide-3'-glucoside (2.14%). Several phenolic acids were identified in these extracts, namely *p*-coumaric acid, vanillic acid, gallic acid, caffeic acid, ferulic acid, syringic acid, sinapic acid, and labiatenic acid. This study also confirmed the results of a previous study of compounds contained in *B. polystachyon*, as shown by the high quantity of phenolic compounds [19-20]. The flavonoid derivatives in the extract were also successfully identified including quercetin, myricetin, kaempferol, apigenin, acacetin, luteolin, hispidulin, hesperetin, velutin, genkwanin, isosakuranetin, ladanein,

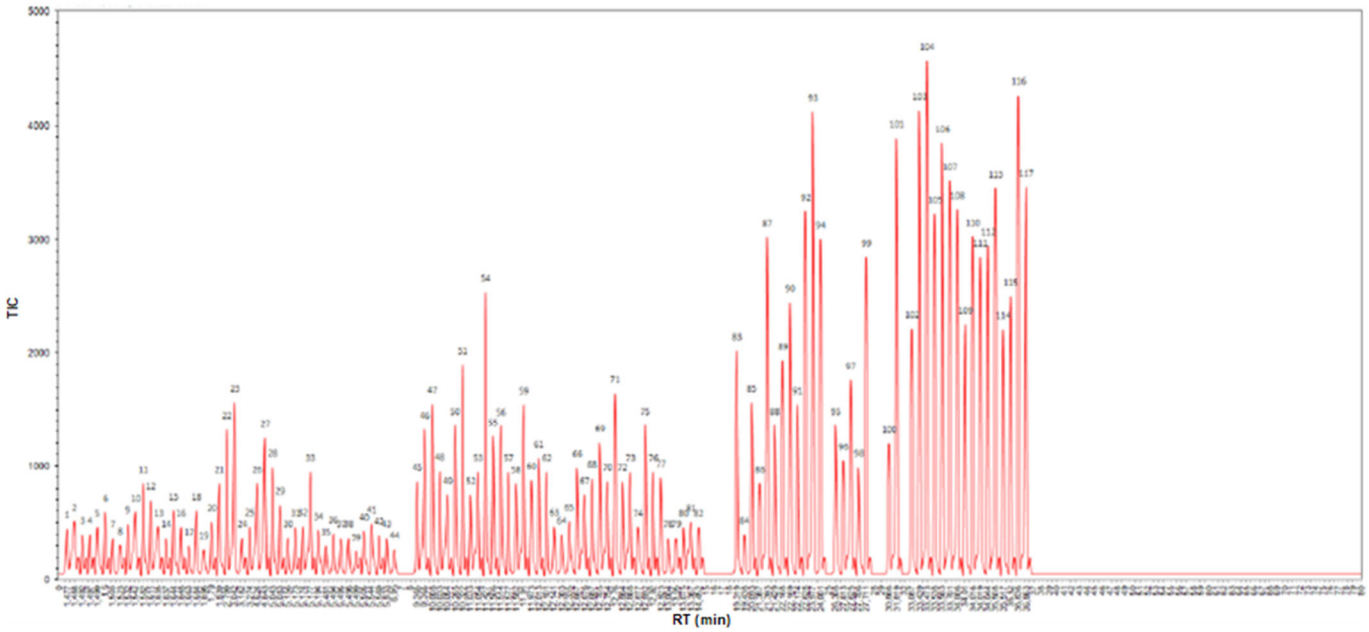


Fig 1. LC-MS chromatogram of the *B. polystachyon* leaf ethyl acetate extract

isokaempferide, eupatorin, nevadensin, salvigenin chrysoeriol, thymonin, and jaceosidin. In addition, ethyl acetate also contains a hydrophobic group in the structure that can bind with non-polar compounds, such as steroids and terpenoids, such as stigmasterol, α-pinene, limonene, α-terpinolene, camphene, α-thujene, β-myrcene, carene, γ-terpinene, α-phellandrene, thymol, borneol, linalool, phellandral, α-terpineol, lavandulol, myrtenol, α-amyrin, β-amyrin, and squalene. The high concentrations of glycoside compounds were found in the extract and became the major compounds appearing on the chromatogram (peaks 85–117). Coumarins, lignans, phenylpropanoids, and polyketides were identified as minor compounds with small percentages in the extracts.

Molecular Docking Simulation

Molecular docking simulations were conducted on the compounds identified by LC-MS in the ethyl acetate extract of *B. polystachyon* leaves to determine their capability as SIRT1 inhibitors. The protein target used in this study was the crystal structure of SIRT1 from *Homo sapiens*. The receptor's active site was identified based on the primary coordinates of the native ligand. The re-docked conformation of the native ligand overlapped with the original conformation before docking simulation with the same ligand-receptor interaction, which is shown in Fig. 2. The RMSD value was determined to be 0.311 Å, indicating that the established docking parameters were capable of reproducing the native conformation.

The results of molecular docking simulation toward SIRT1 enzyme, the native ligand 4I5 as control inhibitor has a binding energy value of −9.21 kcal/mol, with 8 amino acid residues interactions including Ile347 and Asp348 via hydrogen bonds and Phe273, Ile279, Phe297, Ile316, Ile411, Phe413 through hydrophobic interactions. Ile347 and Asp348 are the main catalytic residues of SIRT1 enzyme used to hydrolyze oligosaccharides into glucose molecules. These results are similar to those of a previous study where re-docked native ligands interacted with residues Ile347, Asp348, Ala262, Phe273, Ile279, Phe297, Ile411, and Phe413 [21]. The interactions of these compounds with amino acids present in the binding site may decrease enzymatic activity and inhibit the SIRT1 as a functional protein [22-23]. Ten compounds in the extract had more negative binding energies and lower inhibition constant values than those control inhibitors, indicating that the compounds exhibited promising inhibitory activity towards SIRT1. As shown in Table 1, the binding energy values of these compounds ranged from approximately

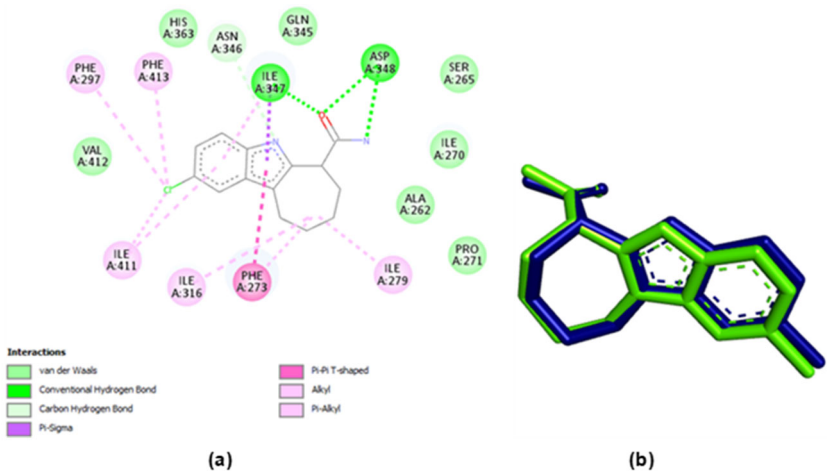


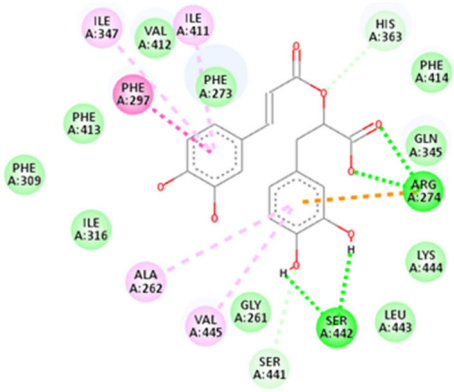
Fig 2. (a) Two-dimensional visualization of interactions of native ligands in the active site and (b) superimposition of the re-docked native ligand (blue) with the crystallographic conformation (green)

Table 1. The binding energy values and inhibition constants of the ligands with receptor

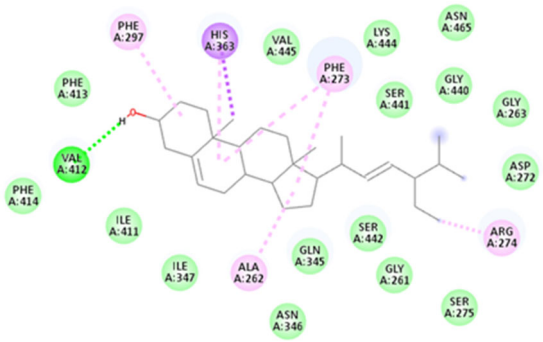
Compounds	Free energy of binding (kcal/mol)	Inhibition constant (Ki) (nM)
Native ligand (4I5)	−9.21	176.07
Lariciresinol	−10.16	35.42
Medioresinol	−10.01	45.75
Olivil	−9.51	106.41
Stigmasterol	−12.16	1.22
Labiatenic acid	−9.21	178.15
Nepetoidin B	−9.97	9.51
Lirioresinol B	−10.37	24.97
[(*Z*)-2-(3,5-dihydroxyphenyl)ethenyl] (*E*)-3-(3,4-dihydroxyphenyl)prop-2-enoate (E1)	−10.36	25.39
4-hydroxyphenethyl (1*R*,4a*S*,7*R*,7a*R*)-1-hydroxy-7-methyl-6-oxo-1,4a,5,6,7,7a-hexahydrocyclopenta[*c*]pyran-4-carboxylate (E2)	−10.65	15.48
3,4-dihydroxyphenethyl (1*R*,4a*S*,7*R*,7a*R*)-1-hydroxy-7-methyl-6-oxo-1,4a,5,6,7,7a-hexahydrocyclopenta[*c*]pyran-4-carboxylate (E3)	−10.22	32.14

−9.21 to −12.16 kcal/mol. Stronger binding and better stability of the ligand-receptor complex formed are generally indicated by a more negative binding energy [21-23]. Thus, the inhibitory activity is more effective, and these compounds can prohibit native substrates from entering the enzyme catalytic sites.

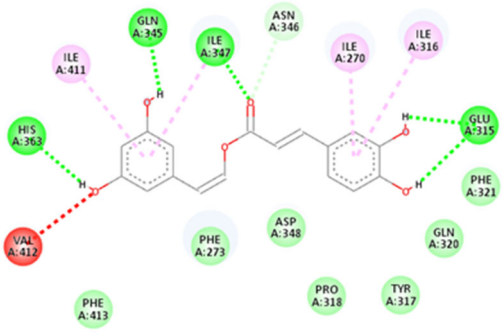
The visualization of 10 potential compounds from molecular docking results is shown in Fig. 3. Fig. 3 illustrates the interactions between the SIRT1 receptor and ligands. Most ligands also bind to identical amino acid residues as native ligands (Ile347, Phe273, and Phe297). The interaction pattern of these compounds was consistent with previous studies indicating that the active site of the SIRT1 included Ile270, Ile316, Ile279, Ile316, Phe273, Phe297, Ile411, Asp348, Asn346, Ile347, Gln345, His363 and Val412 [14]. Several compounds such as labiatenic acid, stigmasterol, medioresinol, olivil, and lariciresinol bind to the same amino acid residue Phe297. Ile347 and Asp348 interacted with the ligand structure through hydrogen bonding by acting as hydrogen atom acceptors. These interactions also occur in the interaction mechanism of the native ligand, E1, and lariciresinol. Meanwhile, the amino acid residues Phe273 and Phe297 interact with the hydrophobic groups on the ligand, including the methyl group and benzene ring. This is due to the similarity of the hydrophobicity of the ligand structure and the amino acid structure that compose the receptor. Stigmasterol has the



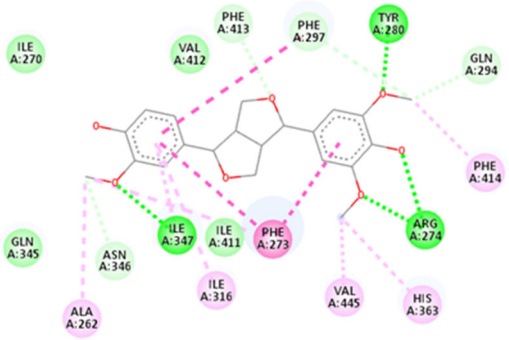
Labiatenic acid



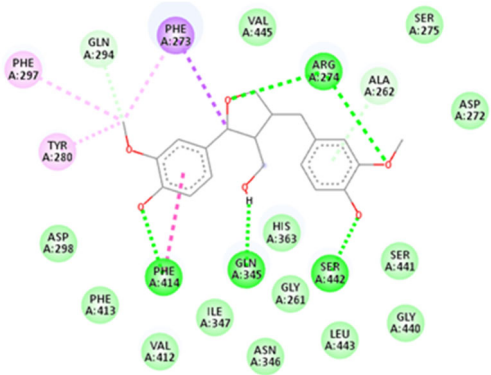
Stigmasterol



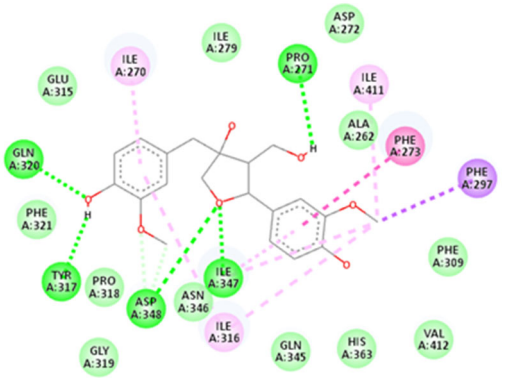
E1



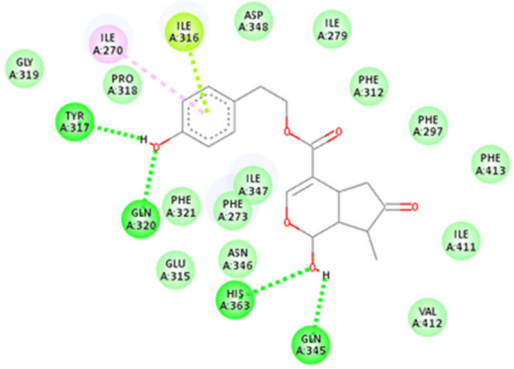
Medioresinol



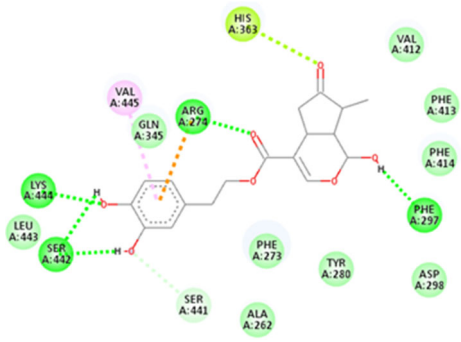
Olivil



Laricresinol



E2



E3

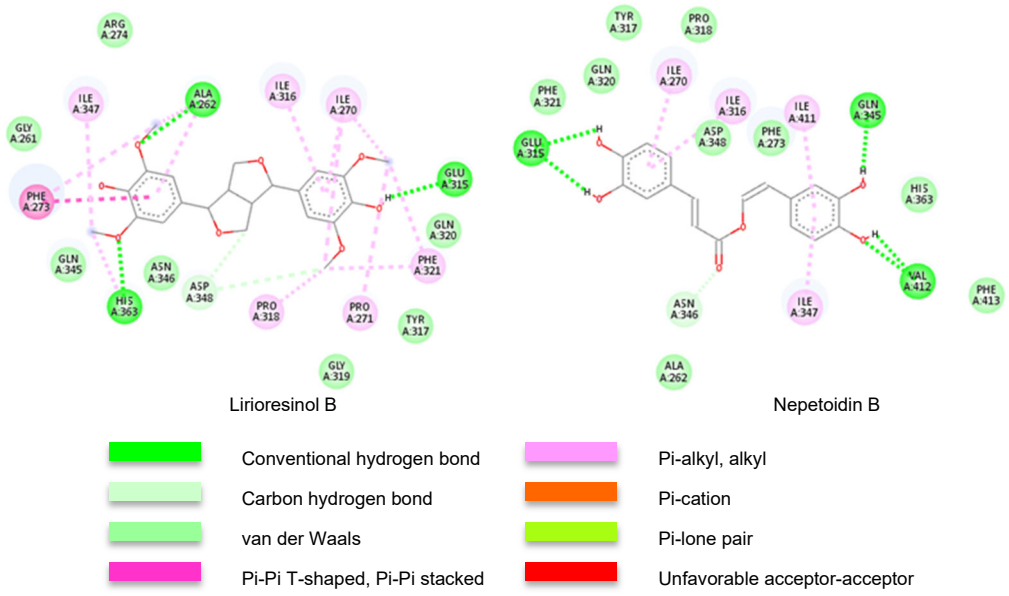


Fig 3. The 2D visualization of the ligand-receptor interactions of potential compounds from the extract with SIRT1 receptor

lowest binding energy values compared to other compounds. Hydrophobic interactions are thought to contribute greatly to the formation of ligand-receptor interactions. Hydrogen bonding and hydrophobic interactions are the main factors influencing ligand binding to the receptor and play a valuable role in the binding energy and strength of the complex. Based on the visualization of ligand and receptor interactions, the potential compounds from *B. polystachyon* mostly interact with the receptor through hydrogen bonds, hydrophobic interactions, and van der Waals forces. However, in this finding, there are types of interactions and amino acid residues that are different from the native ligand interactions. For example, the compound E3 has pi-lone pair and pi-cation electrostatic interactions that are not found in native ligands. Additionally, nepetoidin B and E1 interacted with different residues, such as Glu315, Gln345, Asn346, His363, and Val412. The different interaction patterns were influenced by the structure of the compound and its 3D conformation. However, the different interaction patterns gave lower binding energy values than the control inhibitor, which showed better inhibitory activity. These findings are similar to those of previous studies showing that stigmasterol and labiatenic acid have the capability to inhibit SIRT1 expression [23-24]. Several other compounds, such as lariciresinol and medioresinol, also have been confirmed to act as anticancer agents [25-26].

Drug-likeness, Bioavailability, and Pharmacokinetics Prediction

Predictions of drug-likeness and bioavailability could provide data for predicting the compatibility of 10 compounds in the extract of this plant with good binding energies as medication candidates. The prediction results are summarized in Table 2. Drug-likeness analysis was performed based on Lipinski's rule [27]. The criteria for acceptance of these compounds as drugs based on several rules were as follows: MW < 500 Da, HBD < 5, HBA < 10, and log P < 5. These results suggested that all compounds fulfilled the drug-likeness criteria and could potentially be promising drug candidates. The oral bioavailability prediction was aimed at providing theoretical information on the physicochemical properties. In general, the requirements for a drug candidate to have good oral bioavailability include lipophilicity (−0.7 < Log P < 5.0), size (150 < MW (Da) < 500), polarity (20 < TPSA (Å^2) < 130), and flexibility (0 < number of rotatable bonds < 9). Based on these results, only one compound stigmasterol violated one criterion, which is lipophilicity (Log P: 6.72).

Table 2. Prediction of drug-likeness, bioavailability, and pharmacokinetics of the potential compounds

Compounds	MW (g/mol)	HBA	HBD	MR	Log P	Rot. Bond	TPSA (Å^2)	GI Abs.	B. Score
Lariciresinol	360.40	6	3	97.09	1.17	6	88.38	High	0.55
Medioresinol	388.41	7	2	101.39	0.86	5	86.61	High	0.55
Olivil	376.40	7	4	98.29	0.37	6	108.61	High	0.55
Stigmasterol	412.69	1	1	132.75	6.62	5	20.23	Low	0.55
Labiatenic Acid	360.31	8	5	91.40	0.90	7	144.52	Low	0.56
Nepetoidin B	314.29	6	4	85.14	1.44	5	107.22	High	0.55
Lirioresinol B	418.44	8	2	107.89	0.56	6	95.84	High	0.55
E1	314.29	6	4	85.14	1.44	5	107.22	High	0.55
E2	332.35	6	2	85.34	1.12	5	93.06	High	0.55
E3	348.35	7	3	87.36	0.59	5	113.29	High	0.55

MW-Molecular Weight; HBA-Hydrogen Bond Acceptor; HBD-Hydrogen Bond Donor; MR-Molar Refractivity; Log P-Log Partition; Rot. Bond-Rotatable Bond; TPSA-Topological Polar Surface Area; GI Abs.-Gastrointestinal Absorption; B. Score-Bioavailability Score

It could still be considered to have good potential as an oral drug candidate, as it is usually described as having low compatibility as an oral medication if it does not fulfill multiple criteria [28]. The prediction of the GI absorption parameter showed that those compounds possessed high GI absorption, which meant that compounds could pass through the GI membrane well, except for stigmasterol and labiatenic acid, which showed low GI absorption. This theoretical information can then be used as preliminary data for consideration in the experimental testing.

■ CONCLUSION

This is the first scientific report regarding the identification of the chemical profile in the *B. polystachyon* leaves using LC-MS and the investigation of the anticancer activity in molecular insight towards SIRT1 through computational studies. The identification results showed that the leaves contained phenolics, flavonoids, glycosides, steroids, terpenoids, phenylpropanoids, polyketides, coumarins, and lignans. The molecular docking results revealed 10 compounds with capabilities as SIRT1 inhibitiors. Most of these compounds bind to the same active site of the receptor as a control inhibitor and exhibit lower binding energy. Physicochemical and drug-likeness analyses indicated that all the compounds were potent oral drugs. Hopefully, this research can be used as a reference for discovering potential anticancer drug candidates with inhibition mechanisms on SIRT1. Further research on the isolation of possible compounds, *in vitro* assay toward cancer cells, and their combination with nanomaterials could be an option to continue this research as a solution to breast cancer problems.

■ ACKNOWLEDGMENTS

Gratitude is expressed to the Institute for Research and Community Service for funding support in the 2023 fiscal year through the Rector's Decree Number: 1091/UN38/HK/PP/2023 on June 08, 2023. This research can be supported by the Department of Chemistry, Universitas Negeri Surabaya, for laboratory facilities and other resources and by students of the Universitas Negeri Surabaya.

■ CONFLICT OF INTEREST

The authors have no conflict of interest.

■ AUTHOR CONTRIBUTIONS

Tukiran contributed to the research conception, design, analysis, and manuscript drafting. Muhammad Raihan did molecular docking simulation and data visualization. All the authors have agreed to the final version of this manuscript.

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