© 2026 Journal of Pharmacy & Pharmacognosy Research, 14 (2), 2525, 2026
ISSN 0719-4250
https://jppres.com

DOI: https://doi.org/10.56499/jppres_14.2.2525

Original Article

Targeting PCOS-related inflammation with bioactive compounds of *Syzygium polyanthum* (Wight) Walp. leaves extract: An *in silico* study

[Tratamiento de la inflamación relacionada con el síndrome de ovario poliquístico mediante compuestos bioactivos del extracto de hojas de *Syzygium polyanthum* (Wight) Walp.: un estudio *in silico*]

Renny Aditya[1*], Wirdatun Nafisah[2]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Lambung Mangkurat, Banjarmasin, Indonesia.
[2]Department of Biology, Faculty of Mathematics and Natural Science, Universitas Negeri Surabaya, Indonesia.
*E-mail: dr.rennyaditya@ulm.ac.id

Abstract

Context: Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder affecting reproductive-aged women, often associated with chronic inflammation. The search for novel therapeutic agents has led to the exploration of natural compounds with anti-inflammatory properties. *Syzygium polyanthum*, commonly known as Indonesian bay leaf, is traditionally used in herbal medicine and contains bioactive compounds with potential pharmacological effects.

Aims: To investigate, through *in silico* approaches, the molecular interactions between selected compounds from *S. polyanthum* and inflammatory target proteins relevant to polycystic ovary syndrome therapy.

Methods: Molecular docking analysis was performed using AutoDock Vina integrated with PyRx version 0.8. Additionally, absorption, distribution, metabolism, and excretion (ADME) analysis was conducted to evaluate the pharmacokinetic properties of the selected compounds. The binding affinities of the ligands were evaluated against key inflammatory proteins, namely MMP-9, IL6ST, and HIF-1.

Results: The results suggest that nootkatone exhibits strong binding interactions with inflammatory mediators, indicating its promising potential due to its stable binding affinity in all protein targets (-6.8 kcal/mol in MMP-9; -6.5 kcal/mol in IL6ST; and -7.1 kcal/mol in HIF-1) and favorable pharmacokinetic properties as revealed by ADME analysis, supporting its potential as an anti-inflammatory agents for PCOS management.

Conclusions: These findings suggest that nootkatone may serve as a promising natural anti-inflammatory candidate for the management of polycystic ovary syndrome. Further studies employing molecular dynamics analyses, as well as *in vitro* and *in vivo* experiments, are warranted to validate these results.

Keywords: anti-inflammation; HIF-1; IL6ST; MMP-9; PCOS; *Syzygium polyanthum*.

Resumen

Contexto: El síndrome de ovario poliquístico (SOP) es un trastorno endocrino frecuente que afecta a mujeres en edad reproductiva y suele estar asociado a inflamación crónica. La búsqueda de nuevos agentes terapéuticos ha impulsado la exploración de compuestos naturales con propiedades antiinflamatorias. *Syzygium polyanthum*, comúnmente conocido como laurel indonesio, se utiliza tradicionalmente en la medicina herbal y contiene compuestos bioactivos con potenciales efectos farmacológicos.

Objetivos: Investigar, mediante métodos computacionales, las interacciones moleculares entre compuestos seleccionados de *S. polyanthum* y proteínas inflamatorias diana relevantes para el tratamiento del síndrome de ovario poliquístico.

Métodos: Se realizó un análisis de acoplamiento molecular utilizando AutoDock Vina integrado con PyRx versión 0.8. Además, se realizó un análisis de absorción, distribución, metabolismo y excreción (ADME) para evaluar las propiedades farmacocinéticas de los compuestos seleccionados. Se evaluaron las afinidades de unión de los ligandos frente a proteínas inflamatorias clave, como MMP-9, IL6ST e HIF-1.

Resultados: Los resultados sugieren que la nootkatona presenta fuertes interacciones de unión con mediadores inflamatorios, lo que indica su prometedor potencial debido a su afinidad de unión estable en todas las proteínas diana (-6,8 kcal/mol en MMP-9; -6,5 kcal/mol en IL6ST; y -7,1 kcal/mol en HIF-1) y sus favorables propiedades farmacocinéticas, según lo revelado por el análisis ADME. Esto respalda su potencial como agente antiinflamatorio en el tratamiento del SOP.

Conclusiones: Estos hallazgos sugieren que la nootkatona podría ser un candidato prometedor de tratamiento antiinflamatorio natural para el síndrome de ovario poliquístico. Se justifican estudios adicionales que empleen análisis de dinámica molecular, así como experimentos *in vitro* e *in vivo*, para validar estos resultados.

Palabras Clave: antiinflamación; HIF-1; IL6ST; MMP-9; SOP; *Syzygium polyanthum*.

ARTICLE INFO
Received: July 15, 2025.
Accepted: March 27, 2026.
Available Online: April 14, 2026.

AUTHOR INFO
ORCID: 0000-0001-9731-218X (WN)

Abbreviations: ADME: Absorption, distribution, metabolism, and excretion; BBB: Blood-brain barrier; GI: Gastrointestinal; HIF-1: Hypoxia-inducible factor 1; IL-6: Interleukin 6; IL6ST: Interleukin 6 cytokine family signal transducer; LC-HRMS: Liquid chromatography–high resolution mass spectrometry; MMP-9: Matrix metalloproteinase 9; PCOS: Polycystic ovary syndrome; P-gp: P-glycoprotein; RMSD: Root-mean-square deviation; SMILES: Simplified molecular input line entry system; TPSA: Topological polar surface area; UAE: Ultrasound-assisted extraction.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among women of reproductive age (Zhu et al., 2021), characterized by irregular menstrual cycles, hyperandrogenism, and polycystic ovaries (Hosseinkhani et al., 2018). It is also a leading cause of infertility, accounting for approximately 70% of ovulation-related infertility cases (Wu et al., 2015). The prevalence of PCOS ranges between 6% and 10% in reproductive-aged women (Cai et al., 2023). The exact etiology of PCOS remains complex, as it is influenced by both genetic and environmental factors (Sørensen et al., 2019). In recent years, the incidence of PCOS has been rising significantly, often presenting with comorbid conditions such as diabetes, abnormal uterine bleeding, infertility, and hyperandrogenism (Geng et al., 2019). These complications contribute to a substantial economic burden on both patients and healthcare systems.

Current treatment approaches for PCOS primarily include ovulation-stimulating drugs, insulin sensitizers, and androgen-lowering medications. However, these treatments are often limited to symptomatic management, with frequent relapses upon discontinuation of medication. Additionally, prolonged treatment can lead to adverse effects such as ovarian hyperstimulation syndrome, premature ovarian failure, lactic acidosis, and increased cardiovascular risks (Luo et al., 2022). Thus, there is an urgent need for novel therapeutic strategies that are both effective and safe.

Herbal medicine has been widely explored as a source of bioactive compounds with anti-inflammatory properties. *Syzygium polyanthum* (Wight) Walp. (family *Myrtaceae*) is a prominent species in traditional medicine, known to contain flavonoids, tannins, and essential oils. These bioactive compounds contribute to its diverse pharmacological profile, which includes documented antimicrobial, antihypertensive, and anti-inflammatory (Uddin et al., 2022; Abd Wahab & Ja'afar, 2021). The anti-inflammatory potential of *S. polyanthum* makes it a promising candidate for treating PCOS. This condition is closely linked to chronic low-grade inflammation and oxidative stress, both of which drive insulin resistance and reproductive dysfunction (Rudnicka et al., 2021). Current research indicates that *S. polyanthum* extract can effectively reduce inflammatory markers, such as TNF-α, and increase the count of healthy follicles in PCOS models (Aditya et al., 2023). This suggests a viable natural therapy with fewer side effects compared to synthetic drugs.

The exploration of its anti-inflammatory activity in PCOS provides scientific validation of long-standing ethnomedical claims. Traditionally, *S. polyanthum* has been utilized to manage hypertension, diabetes, and various inflammatory conditions (Abdulrahman, 2023). Its efficacy as a healing agent is driven by its secondary metabolites, particularly terpenoids, sesquiterpenes, and triterpenoids (Ismail & Wan Ahmad, 2019). Despite its widespread ethnomedical use, the specific molecular mechanisms by which *S. polyanthum* modulates inflammatory pathways in PCOS remain largely unexplored. This study aims to systematically investigate the link between specific compounds, such as nootkatone and oleanolic acid derivatives, and the modulation of these pathways. Filling this knowledge gap is critical to the development of new phytopharmaceuticals to advance women's reproductive health management.

Molecular docking analysis is a powerful computational tool for predicting the binding affinity and interactions of these compounds with key inflammatory proteins involved in PCOS. This study was undertaken to prioritize *S. polyanthum* metabolites with predicted anti-inflammatory activity relevant to PCOS. Compounds derived from *S. polyanthum*, particularly nootkatone, are hypothesized to exhibit strong binding affinities for key inflammatory mediators, including matrix metalloproteinase 9 (MMP-9), interleukin 6 cytokine family signal transducer (IL6ST), and hypoxia-inducible factor 1 (HIF-1), thereby presenting promising natural therapeutic candidates for the management of PCOS-related inflammation.

MATERIAL AND METHODS

Plant material collection and identification

The leaves of *S. polyanthum* were obtained from UPT Balai Materia Medika, East Java, Indonesia, located at GPS coordinates 7°52'01.2"S and 112°31'13.2"E. Botanical identification and authentication were performed by the same institution (Determination No. 074/629/102.7-A/2021), where a representative voucher specimen has been deposited. Prior to extraction, the plant material was cleaned, air-dried at room temperature, and ground into a fine powder.

Ultrasound-assisted extraction (UAE)

The bioactive compounds were extracted using UAE (Medina-Torres et al., 2017). The dried leaf powder was submerged in 96% ethanol at a 1:10 (m:v) ratio. The mixture was subjected to ultrasonic waves using a SONICA Ultrasonic Cleaner, model SONICA® 2400EP S3 (Soltec Soluzioni Technologiche, Italy), at a power setting of 2400W for 30 minutes at room temperature, with stirring every 10 minutes (Jabbari et al., 2024). The resulting extract was filtered and concentrated using a rotary evaporator at 50°C, 70 rpm, followed by oven drying at 40°C. The extract was stored at 4°C until further use.

Liquid chromatography–high resolution mass spectrometry (LC-HRMS) analysis and compound identification

The chemical profile of the *S. polyanthum* extract was analyzed using LC-HRMS (Peñaloza et al., 2020). Chromatographic separation was achieved using a Hypersil GOLD aQ 50 × 1 mm × 1.9 µm particle size column with a flow rate of 40 µL/min, a run time of 30 min, and a column oven temperature of 30°C. The LC-HRMS instrument was a Thermo Scientific Dionex Ultimate 3000 RSLCnano, coupled with a Thermo Scientific Q Exactive mass spectrometer operating in both positive and negative ionization modes. Mass spectra were acquired at 70,000 resolution (full scan) and 17,500 resolution (MS2). Raw data were processed using Compound Discoverer Software (Thermo Scientific), and metabolites were identified by comparison with the mzCloud MS/MS Library.

Target protein determination

The protein target prediction for each compound from *S. polyanthum* was performed using Swisstarget (http://www.swisstargetprediction.ch/). The SMILES of each compound were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and used for target identification. The results of the analysis were obtained and saved in an Excel format for further analysis.

PCOS database exploration

Proteins related to PCOS were explored by extracting all proteins listed in the database of PCOS (http://doc.pcosbase.org/pcos-networks/). These proteins were then intersected with the predicted protein target of *S. polyanthum*'s compounds using a Venn diagram tool (https://bioinfogp.cnb.csic.es/tools/venny/index.html).

Data mining and preparation

Three target proteins were selected based on the target identification results: IL6ST (ID: 1P9M), MMP-9 (ID: 4WZV), and HIF-1 (ID: 3KCX). The selected PDB structures were carefully examined to ensure that they represented biologically relevant and druggable domains. The structure 1P9M corresponds to the extracellular domain of IL6ST (gp130) involved in ligand binding and signal transduction. The HIF-1 structure (3KCX) represents the PAS-B domain of HIF-1α, which contains a ligand-binding cavity previously reported as a potential small-molecule binding site. Structural completeness, resolution (<3.0 Å), and presence of co-crystallized ligands were considered before docking.

The 3D structures of the proteins were obtained from the RCSB PDB database (https://www.rcsb.org/) in .pdb format. The bioactive compounds targeting these three proteins, based on the previous identification target results, were selected as ligands. Meanwhile, the control inhibitors for each protein were E40 for MMP-9, bazedoxifene for IL6ST, and clioquinol for HIF-1. The 3D structures, SMILES, and IDs of each selected compound from *S. polyanthum*, along with the control inhibitors, were retrieved through the PubChem database in .sdf format file (Table 1).

Ligand and protein preparations were performed before docking. Selected ligands or bioactive compounds were prepared in OpenBabel, integrated with PyRx v.0.8 (O'Boyle et al., 2011), using energy minimization. Protein preparation was performed using PyMOL (Schrödinger, LLC, 2015) by removing water molecules and previously bound ligands, and the resulting structure was saved in .pdb format.

Protein preparation and active-site refinement

Protein preparation was performed using AutoDock Tools 1.5.7 software (Morris et al., 2009). The process involved the removal of water molecules and previously bound co-crystallized ligands, followed by the addition of polar hydrogen atoms. For the MMP-9 structure (PDB ID: 4WZV), specific measures were taken to preserve metal ions within the active site. The catalytic zinc ion (Zn^{2+}) and structural calcium ions (Ca^{2+}) were explicitly retained to preserve the biological integrity of the binding pocket, as these ions are critical for inhibitor coordination. The proteins were then assigned Gasteiger charges and saved in .pdbqt format for subsequent docking simulations.

Table 1. Small molecules evaluated in molecular docking.

No	Name	CID	Formula	SMILES
1	Deoxyphomalone	26470515	$C_{13}H_{18}O_4$	CCCC(=O)C1=C(C=C(C(=C1O)CC)O)OC
2	(+)-ar-Turmerone	160512	$C_{15}H_{20}O$	CC1=CC=C(C=C1)[C@@H](C)CC(=O)C=C(C)C
3	Sclareol (318237-79-5)	521332	$C_{20}H_{36}O_2$	CC1(CCCC2(C1CCC(C2CCC(C)(C=C)O)(C)O)C)C
4	Nootkatone	1268142	$C_{15}H_{22}O$	C[C@@H]1CC(=O)C=C2[C@]1(C[C@@H](CC2)C(=C)C)C
5	Caryophyllene oxide	1742210	$C_{15}H_{24}O$	C[C@@]12CC[C@@H]3[C@H](CC3(C)C)C(=C)CC[C@H]1O2
6	Oleanolic acid	10494	$C_{30}H_{48}O_3$	C[C@]12CC[C@@H](C([C@@H]1CC[C@@]3([C@@H]2CC=C4[C@]3(CC[C@@]5([C@H]4CC(CC5)(C)C)C(=O)O)C)C)(C)C)O
7	CHEBI:189401	9421722	$C_{20}H_{30}N_2O_3S$	CCCS(=O)(=O)N1C[C@@H]2C[C@H](C1)C3=CC=C(C(=O)N3C2)C4CCCCC4

Table 2. Grid box for docking analysis.

Target protein	Grid	Control inhibitor
MMP-9	Center X: 2.3644; Y: 8.1363; Z: 22.7722 Dimension (A): X: 17.1818; Y: 13.4052; Z: 15.0640	E40
IL6ST	Center X: -88.153; Y: 185.793; Z: 50.9779 Dimension (A): X: 15.0063; Y: 15.5792; Z: 13.2662	Bazedoxifene
HIF-1	Center X: -20.859; Y: 24.7614; Z: 7.4875 Dimension (A): X: 9.6844; Y: 7.4690; Z: 10.3317	Clioquinol

Molecular docking and results visualization

Molecular docking was performed using AutoDock Vina (Trott & Olson, 2010) integrated with PyRx v.0.8 (Dallakyan & Olson, 2015) by submitting files for all selected compounds and macromolecules (proteins). Subsequently, molecular docking was performed on the prepared proteins and ligands using identical grid box coordinates derived from the control inhibitor for each protein target (Table 2).

Docking protocol validation

Prior to screening test ligands, the docking protocol was validated by redocking the native (co-crystallized) ligands into their respective binding sites on the target proteins. The accuracy of the docking parameters was assessed by calculating the root-mean-square deviation (RMSD) between the predicted pose and the original experimental (crystallographic) pose. An RMSD value of less than 2.0 Å was considered acceptable, confirming that the docking parameters, including grid center, box size, and exhaustiveness, were reliable for further simulations. To ensure high sampling accuracy and consistency, the exhaustiveness parameter was set to 8. These validated parameters were then applied uniformly to all test ligands. The docking results were then analyzed and visualized in Biovia Discovery Studio 2019 (BIOVIA, 2019) to identify the binding types and residues involved in the interactions. The 3D complex and 2D interactions were recorded and saved.

Absorption, distribution, metabolism, and excretion (ADME) prediction

The potential compound candidates were assessed for drug-likeness using Lipinski's rule of five using the web server SwissADME (http://www.swissadme.ch) (Daina et al., 2017). The evaluation included key parameters: molecular weight (≤500 Da), lipophilicity (LogP ≤5), hydrogen-bond donors (≤5), hydrogen-bond acceptors (≤10), and topological polar surface area (TPSA). The scores of each parameter were then collected and considered in the evaluation of drug potential.

In silico analytical standards

In this study, inferential statistical analysis was not applicable because the data were generated through deterministic computational simulations rather than stochastic biological observations. The reliability and significance of the results were ensured through several analytical standards. First, the precision of the molecular docking method was validated using RMSD analysis, with a threshold of <2.0 Å for accuracy. Second, binding affinities were expressed as free

energy (kcal/mol), and the most stable ligand-protein complexes were selected based on the lowest binding energy values across multiple runs (exhaustiveness set to 8). Third, small-molecule drug-likeness was assessed using the Lipinski Rule of Five, ensuring that only viable therapeutic candidates were considered. Finally, the interactions of *S. polyanthum* compounds were compared against native ligands and established reference compounds to determine their relative inhibitory or activatory potential.

Ethics statement

No human or animal experiments were involved in this study. Ethical approval was therefore not applicable.

RESULTS

Compounds contained in *S. polyanthum* extract

Based on LC-HRMS analysis, the bioactive compounds contained in *S. polyanthum* included deoxyphomalone, (+)-ar-turmerone, sclareol (318237-79-5), nootkatone, caryophyllene oxide, oleanolic acid, and CHEBI:189401 with retention times of 14.707, 17.422, 22.225, 17.663, 16.566, 20.784, and 0.923, respectively. The overall chromatogram of *S. polyanthum* bioactive compounds is shown in Fig. 1.

Protein target prediction

Swiss-Target Prediction identified 356 protein targets for *S. polyanthum* compounds, which were intersected with 8,172 proteins from the PCOS database. A total of 190 proteins overlapped between the PCOS database and the protein targets of compounds (Fig. 2). Based on the literature, three anti-inflammatory proteins were selected: MMP-9, IL6ST, and HIF-1. These proteins are known to play a crucial role in inflammatory pathways associated with PCOS (Goodarzi et al., 2011).

Molecular docking analysis

Molecular docking analysis showed that seven bioactive compounds exhibited varying binding affinity scores for the selected target proteins (Table 3). The docking results indicate that CHEBI:189401 had the highest binding affinity for MMP-9 (-9.4 kcal/mol), similar to that of the E40 control inhibitor (-9.9 kcal/mol), suggesting strong inhibitory potential against this enzyme.

Meanwhile, for the IL6ST protein, oleanolic acid exhibited the lowest binding affinity, at -8 kcal/mol, even lower than that of its control, bazedoxifene (-7.7 kcal/mol). In contrast, for the HIF-1 protein, caryophyllene oxide had the lowest binding affinity at -7.2 kcal/mol, which exhibited stronger binding affinity than its control, clioquinol (-6.3 kcal/mmol).

However, after aligning all the results, nootkatone has quite a stable binding score affinity in all of the protein targets, with scores of -6.8 kcal/mol (MMP-9-nootkatone), -6.5 kcal/mol (IL6ST-nootkatone), and -7.1 kcal/mol (HIF-1-nootkatone), making it a particularly promising candidate for further investigation. Although its binding affinity is not the strongest among the tested compounds, its consistency across multiple targets suggests a broader potential interaction profile.

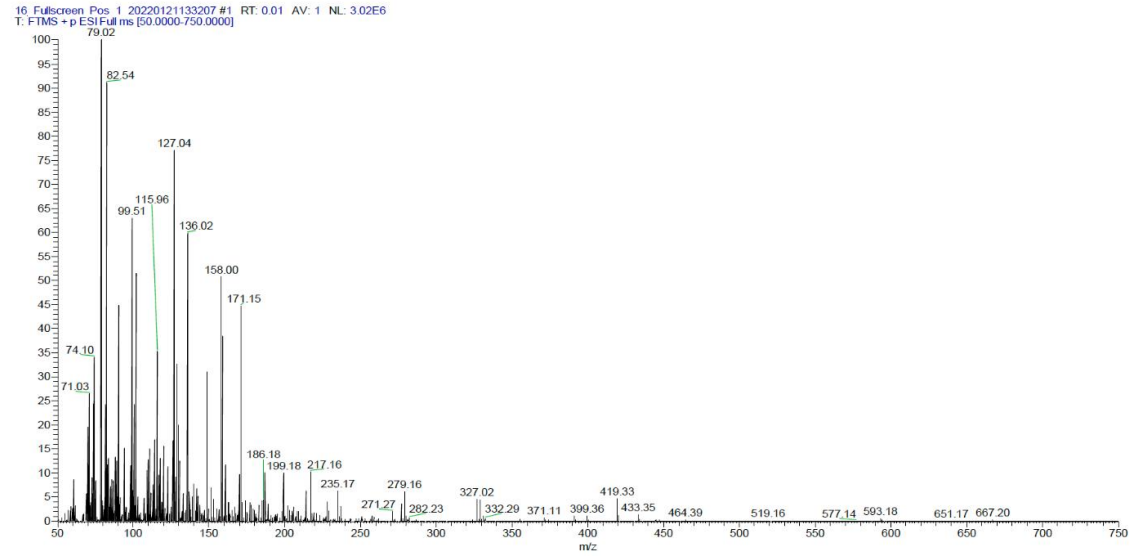

Figure 1. Bioactive compounds *S. polyanthum* chromatogram obtained by LC-HRMS analysis.

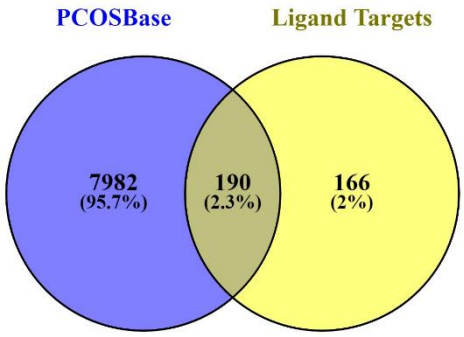

Figure 2. Intersection analysis between predicted targets of *Syzygium polyanthum* metabolites and PCOS-associated proteins.

A total of 356 predicted targets were intersected with 8,172 PCOS-related proteins curated from PCOSBase, yielding 190 overlapping proteins. Three inflammation-related proteins (MMP-9, IL6ST, and HIF-1) were selected for docking analysis based on literature-supported relevance to PCOS-associated inflammatory signaling.

Table 3. Molecular docking results of three target proteins towards seven potential compounds.

Receptor	Ligand	Binding affinity (kcal/mol)
MMP-9	E40 (control inhibitor)	-9.9
	CHEBI:189401	-9.4
	(+)-ar-Turmerone	-8
	Deoxyphomalone	-6.9
	Oleanolic acid	-6.8
	Nootkatone	-6.8
	Caryophyllene oxide	-6.6
	Sclareol (318237-79-5)	-6.6
IL6ST	Oleanolic acid	-8
	Bazedoxifene (Control inhibitor)	-7.7
	Sclareol (318237-79-5)	-7.4
	CHEBI:189401	-6.6
	Nootkatone	-6.5
	Caryophyllene oxide	-6.4
	Deoxyphomalone	-5.6
	(+)-ar-Turmerone	-5.4
HIF-1	Caryophyllene oxide	-7.2
	Nootkatone	-7.1
	(+)-ar-Turmerone	-6.7
	Sclareol (318237-79-5)	-6.6
	Clioquinol (control inhibitor)	-6.3
	Deoxyphomalone	-6.2
	CHEBI:189401	-2
	Oleanolic acid	-5.2

To further understand its molecular interactions, the binding mechanisms of nootkatone with target proteins were analyzed. Visualization of the docked complexes revealed that nootkatone formed hydrogen bonds, hydrophobic bonds, and van der Waals interactions with key residues in the active sites of the target proteins (Fig. 3).

The complexes between nootkatone and the target proteins exhibit strong interactions, with each forming hydrogen bonds. MMP-9-nootkatone had relatively good hydrophobicity as shown by the brown color, and the complex forms hydrogen bonds with THR 130, hydrophobic bonds with PRO 157 and PHE 136, and van der Waals interaction with PRO 104, ARG 128, GLY 127, GLY 126, THR 158, GLU 129, ARG 154, THR

156, ASN 135, and THR 134. IL6ST-nootkatone had relatively low hydrophobicity, as indicated by the white-to-blue color change, but the complex retained hydrogen bonds (namely THR 130), along with two hydrophobic bonds and 10 van der Waals interactions. While HIF-1-nootkatone also showed good hydrophobicity and maintained some of the interacting residues, such as hydrogen bonds in ASN 205, hydrophobic bonds in PHE 207, LEU 188, TYR 145, TRP 296, and HIS 199, as well as van der Waals interactions in LYS 214, ILE 281, ASN 294, LEU 186, THR 196, GLN 147, TYR 102, ASP 201, HIS 279, and ILE 273.

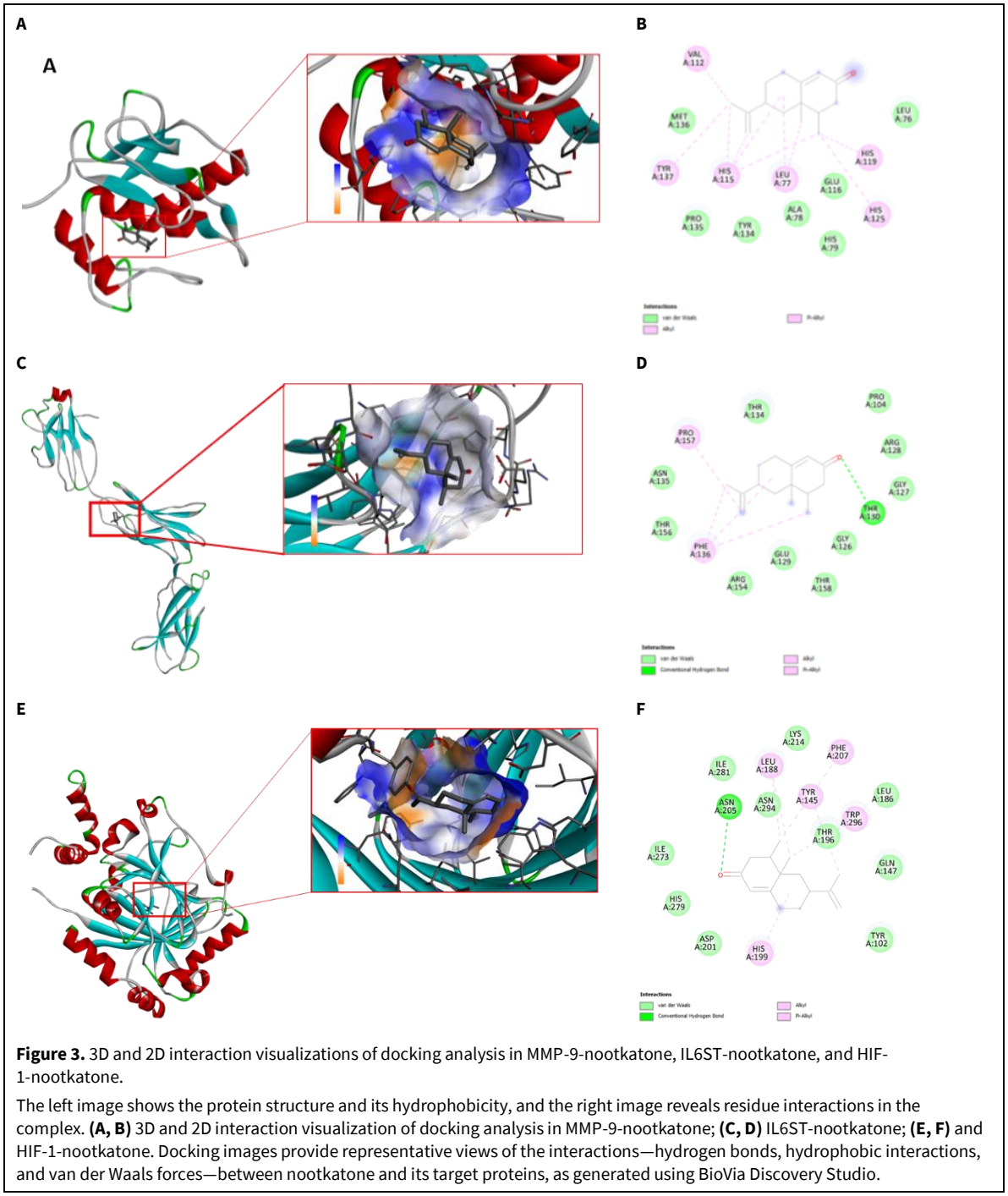

Figure 3. 3D and 2D interaction visualizations of docking analysis in MMP-9-nootkatone, IL6ST-nootkatone, and HIF-1-nootkatone.

The left image shows the protein structure and its hydrophobicity, and the right image reveals residue interactions in the complex. **(A, B)** 3D and 2D interaction visualization of docking analysis in MMP-9-nootkatone; **(C, D)** IL6ST-nootkatone; **(E, F)** and HIF-1-nootkatone. Docking images provide representative views of the interactions—hydrogen bonds, hydrophobic interactions, and van der Waals forces—between nootkatone and its target proteins, as generated using BioVia Discovery Studio.

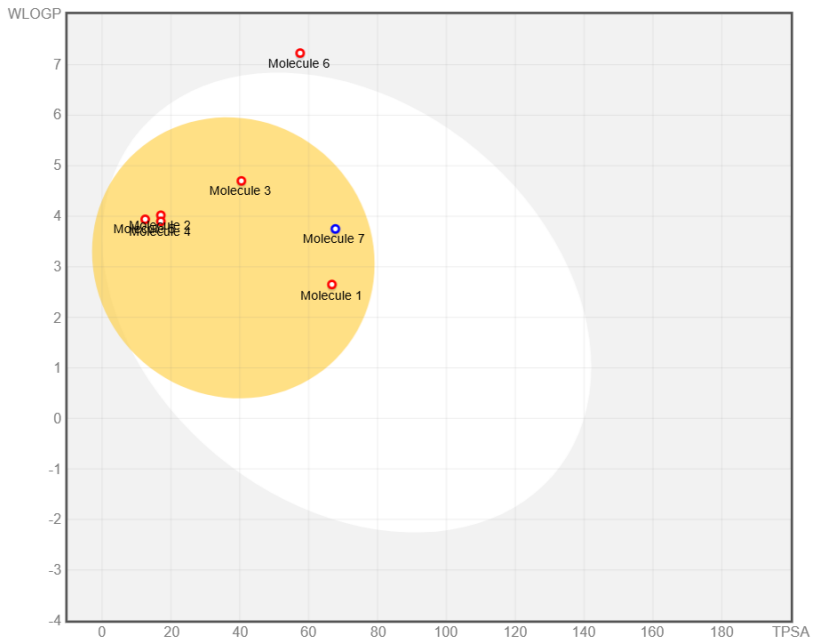

Figure 4. BOILED-Egg model for the pharmacokinetic evaluation of bioactive compounds.

The BOILED-Egg plot illustrates the gastrointestinal (GI) absorption and blood-brain barrier (BBB) permeation of the identified molecules based on their lipophilicity (WLOGP) and polarity (TPSA). Molecules located within the yellow region (yolk), such as nootkatone (molecule 4), are predicted to have high GI absorption and the ability to permeate the BBB. Molecules in the white region indicate high GI absorption but are non-permeant to the BBB. Points located outside the egg, like molecule 6, suggest low GI absorption. The blue dots (like on molecule 7) represent molecules predicted to be actively effluxed by P-glycoprotein (P-gp), while red dots indicate non-substrates of P-gp.

Table 4. Pharmacokinetic properties and drug-likeness evaluation of *S. polyanthum* bioactive compounds based on SwissADME analysis.

No.	Molecule	MW	WLOGP	H-bond donors	H-bond acceptors	TPSA	ESOL Class	GI absorption	BBB permeant	Lipinski violations
1	Deoxyphomalone	238.28	2.65	2	4	66.76	Soluble	High	Yes	0
2	(+)-ar-Turmerone	216.32	4.02	0	1	17.07	Soluble	High	Yes	0
3	Sclareol (318237-79-5)	308.5	4.7	2	2	40.46	Moderately soluble	High	Yes	0
4	Nootkatone	218.33	3.9	0	1	17.07	Soluble	High	Yes	0
5	Caryophyllene oxide	220.35	3.94	0	1	12.53	Soluble	High	Yes	0
6	Oleanolic acid	456.7	7.23	2	3	57.53	Poorly soluble	Low	No	1
7	CHEBI:189401	378.53	3.75	0	4	67.76	Moderately soluble	High	Yes	0

ADME analysis prediction

The pharmacokinetic evaluation highlights nootkatone (molecule 4) as a standout candidate with a superior drug-likeness profile (Table 4). With a molecular weight of 218.33 g/mol, it falls well within the ideal range for oral bioavailability, adhering strictly to Lipinski's Rule of Five. This small molecular size, combined with a TPSA of 17.07 Å², facilitates efficient passive diffusion through biological membranes.

The BOILED-Egg model (Fig. 4) provides critical insights into its physiological distribution. Nootkatone is located within the yellow region (yolk), indicating a unique dual capability: high gastrointestinal (GI) absorption and successful permeation across the blood-brain barrier (BBB) (Table 4). This suggests that nootkatone not only possesses high oral bioavailability but also the potential for central nervous system activity, which is significant for systemic therapeutic applications. Furthermore, as a red dot in the model, nootkatone is identified as a non-substrate for P-glycoprotein (P-gp). This lack of interaction with P-gp efflux pumps prevents the compound from being actively pumped out of cells or the brain, thereby maintaining effective therapeutic concentrations in target tissues.

In terms of lipophilicity, nootkatone's WLOGP of 3.90 reflects a balanced amphiphilic nature, which is further supported by its "soluble" status in the ESOL classification. This solubility is crucial for drug formulation, ensuring that the compound can be effectively dissolved and absorbed in the GI tract. Compared with other compounds such as oleanolic acid (molecule 6), which exhibits poor solubility and low GI absorption, nootkatone's pharmacokinetic profile is significantly more favorable for drug development. These integrated findings reinforce the potential of nootkatone as

a highly bioavailable lead compound for managing complex conditions such as PCOS.

DISCUSSION

This study highlights the potential of *S. polyanthum* compounds in targeting inflammatory pathways associated with PCOS. The molecular docking results indicate that *S. polyanthum* compounds possess significant binding affinity towards inflammatory mediators in PCOS, suggesting their potential as therapeutic agents. Among the compounds from *S. polyanthum*, nootkatone exhibited relatively stable binding affinities across all target proteins, with binding affinity scores of -6.8 kcal/mol for MMP-9, -6.5 kcal/mol for IL6ST, and -7.1 kcal/mol for HIF-1.

The visualization of docked complexes revealed that nootkatone formed hydrogen bonds, hydrophobic interactions, and van der Waals forces with key residues in the active sites of MMP-9, IL6ST, and HIF-1, contributing to its stability and potential inhibitory activity. Specifically, hydrogen bonds were observed with THR 130 in MMP-9, THR 130 in IL6ST, and ASN 205 in HIF-1. Hydrogen bonds in the protein-ligand complex influence the stability and energy requirements of the protein-ligand interaction (Chen et al., 2016). Hydrogen bonds provide strong attractive forces between proteins and ligands via functional groups such as carboxyl, amino, or hydroxyl (Hutchins, 2018). Remarkably, hydrogen bonds are the primary interaction type for inhibitors in the PDB database (Freitas & Schapira, 2017), suggesting the significant role of this interaction in the discovery of protein antagonists. These interactions suggest that nootkatone can effectively bind to and possibly modulate the activity of these inflammatory proteins.

MMP-9-nootkatone and HIF-1-nootkatone complexes exhibited good hydrophobicity, as evidenced by their brown color (Fig. 3). The hydrophobic surface of the binding site contributes to the stability of protein-ligand interaction. The surface hydrophobicity of proteins, which also commonly serve as ligand-binding pockets, contributes to their protein-ligand stability and flexibility (Lee & Barron, 2017). In addition to polar interactions, the proteins' hydrophobic surfaces also contribute to their thermodynamic stability (Ferenczy & Kellermayer, 2022). Thus, binding of the compounds to the hydrophobic regions of the proteins stabilizes interactions and enables their bioactivity.

Notably, its high GI absorption and BBB permeability indicate it may be efficiently absorbed and distributed throughout the body. Furthermore, nootkatone adheres to Lipinski's Rule of Five, ensuring good drug-likeness and bioavailability. Given its strong binding interactions and pharmacokinetic properties, nootkatone may act as a modulator of inflammatory pathways associated with PCOS.

MMP-9, a matrix metalloproteinase synthesized by the ovary, plays a vital role in different stages of female reproduction. In PCOS, elevated MMP-9 levels negatively affect ovulation and fertility by disrupting extracellular matrix remodeling (Sylus et al., 2020). This imbalance leads to abnormal follicular atresia and increased ovarian stromal tissue, further contributing to reproductive dysfunction (Nissi et al., 2013). It is suggested that follicular growth and structural remodeling within the ovarian microenvironment are regulated by a dynamic balance between MMP activity and the levels of their natural inhibitors, TIMPs (Ranjbaran et al., 2016). These findings underscore the importance of further exploring MMP-9 as a potential therapeutic target in the management of PCOS-related infertility.

IL6ST, also known as glycoprotein 130 (gp130), is a transmembrane protein that is part of the IL-6 receptor family. A significant number of studies have estimated IL-6 levels in association with PCOS (Borthakur et al., 2020). This is reasonable, given evidence of elevated cytokine levels, especially IL-6, in numerous murine models and human subjects. The data support the idea that targeted inflammatory trajectories can help ameliorate the disease condition. The positive response of IL-6-targeting drugs in cancer suggests that they may be effective for other inflammatory conditions. Studies on PCOS have already demonstrated its inflammatory nature, and thus IL-6 signaling may play a very important role in identifying treatment strategies (Borthakur et al., 2020).

In inflammatory PCOS, HIF-1 acts as a key transcription factor activated under low-oxygen conditions, leading to the upregulation of genes involved in inflammation, angiogenesis, and metabolic dysregulation, contributing to the chronic inflammatory state observed in the syndrome. Extensive research has been conducted on PCOS pathogenesis and treatment strategies. It has been clearly demonstrated that the HIF-1α signaling pathway plays an important regulatory role during this process (Tang et al., 2021; Wang et al., 2015; 2017; 2022). Notably, HIF-1α appears to be essential in the therapeutic effects of dimethyldiguanide (DMBG), positioning it as a promising target for novel PCOS treatments (Lebinger, 2007; Naseri et al., 2023; Wang & Wu, 2020). By targeting these proteins, nootkatone could mitigate inflammatory responses and improve outcomes in PCOS-related complications.

However, it is important to acknowledge the limitations of *in silico* predictions. Furthermore, docking studies assume rigid receptor conformations and may not fully account for protein flexibility, solvent effects, and entropic contributions. Metalloprotein

coordination geometry, especially in MMP-9, may also limit scoring accuracy. Therefore, the reported binding energies should be interpreted as relative estimates rather than absolute affinity values. Molecular docking and ADME analysis provide valuable preliminary insights but do not fully capture the dynamic physiological environment, including protein flexibility, metabolism, and systemic interactions.

Therefore, these findings should be considered hypothesis-generating rather than conclusive and require validation through molecular dynamics simulations, *in vitro* assays, and *in vivo* studies. Future work should incorporate molecular dynamics simulations to assess the stability of protein–ligand interactions, *in vitro* assays such as nitric oxide inhibition and cytokine modulation in PCOS-like cell lines, and comparative studies with established anti-inflammatory phytochemicals, such as curcumin and resveratrol. Furthermore, synergistic modeling of nootkatone with standard PCOS drugs, such as metformin, may provide insights into potential combination therapies. Taken together, exploring the synergy between these bioactive molecules and established PCOS therapies could open the door to more effective treatment strategies.

Compared to current PCOS therapies such as ovulation-inducing agents, insulin sensitizers, and androgen-lowering medications (Melin et al., 2024; Singh et al., 2023), nootkatone offers a distinct mechanism of action by targeting inflammatory mediators (Dantas et al., 2020). Conventional drugs mainly target hormonal imbalance and metabolic dysfunction, but often cause relapse or adverse effects after discontinuation. In contrast, natural compounds like nootkatone may provide complementary anti-inflammatory benefits, potentially reducing side effects and enhancing long-term management when used alongside standard therapies.

Taken together, this study prioritizes nootkatone as a multi-target candidate based on docking consistency rather than absolute binding strength, supporting its selection for downstream experimental validation rather than immediate therapeutic translation.

CONCLUSION

This study highlights the potential of compounds from *Syzygium polyanthum* as anti-inflammatory agents for PCOS therapy. Nootkatone was identified as a particularly promising candidate due to its stable binding affinity and favorable pharmacokinetic properties. Future experimental validation through *in vitro* and *in vivo* studies is necessary to confirm its efficacy and safety.

CONFLICT OF INTEREST

The research was conducted entirely free from any involvement in commercial, financial, or personal matters that might be perceived as a possible conflict of interest or that could have influenced the outcomes or interpretation of the study.

DATA AVAILABILITY

All data supporting the findings of this study are available from the corresponding author upon reasonable request.

ACKNOWLEDGMENTS

The authors acknowledge the support of the Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Lambung Mangkurat, Banjarmasin, Indonesia. This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

GENERATIVE ARTIFICIAL INTELLIGENCE (AI)

The authors used Microsoft Copilot to improve the language and readability of the manuscript. The authors reviewed and edited the content and take full responsibility for its accuracy. No images were generated or manipulated using AI tools.

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AUTHOR CONTRIBUTION:

Contribution	Aditya R	Nafisah W
Concepts or ideas	x	
Design	x	
Definition of intellectual content	x	
Literature search		x
Experimental studies		x
Data acquisition		x
Data analysis		x
Statistical analysis	x	
Manuscript preparation	x	x
Manuscript editing	x	x
Manuscript review	x	x

Citation Format: Aditya R, Nafisah W (2026) Targeting PCOS-related inflammation with bioactive compounds of *Syzygium polyanthum* (Wight) Walp. leaves extract: An *in silico* study. J Pharm Pharmacogn Res 14(2): 2525. https://doi.org/10.56499/jppres_14.2.2525

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