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Research Article

Phytochemical Compounds Identification From 70% Ethanol Extract of *Arcangelesia Flava* (L.) Merr Stems Using LC-MS/MS and *In-Silico* Molecular Docking Approach as Inhibitor Interleukin-1β

Rizki Rahmadi Pratama[1], Irawati Sholikhah[2], Sukardiman[3], Ram Kumar Sahu[4], Retno Widyowati[3,*]

ABSTRACT

Arcangelisia flava (L.) Merr has been traditionally used to treat jaundice, liver disease, diarrhea, fever, and inflammation. Judging from its potential, scientific evidence of this plant extract as an inhibitor of interleukin-1 β is still lacking. This study aims to investigate the phytochemical compounds present in the 70% ethanol extract of *Arcangelesia flava* stems by LC-MS/MS and to elucidate the ligand-protein interactions through *in-silico* studies. The extract was found to contain alkaloids, flavonoids, furano-diterpene, hydroxyquinoline, phenylpropanoid, phenol, and fatty acids. According to molecular docking of the 15 compounds analyzed by LC-MS/MS, the compounds 3-hydroxy-3',4',5'-trimethoxyflavone (ΔG=-7.72 kcal/mol), fisisaine (ΔG=-6,91 kcal/mol), and demethyleneberberine (ΔG=-6.85 kcal/mol), which demonstrated the highest affinity for binding to the protein target. In addition, active amino acids contribute to this interaction by creating strong hydrogen bonds, such as MET148, LYS 103, and THR300. Phytochemical compounds from *Arcangelesia flava* may serve as adjunctive therapy or a promising source of advanced structures in drug discovery for treatments targeting interleukin-1 β .

Key words: *Arcangelisia flava* (L.) Merr, Inhibitor interleukin-1 β , lc-ms/ms, Molecular docking.

Rizki Rahmadi Pratama[1], Irawati Sholikhah[2], Sukardiman[3], Ram Kumar Sahu[4], Retno Widyowati[3,*]

[1]*Master Program of Pharmaceutical Sciences, Faculty of Pharmacy, Airlangga University, Surabaya, INDONESIA.*

[2]*Department of Chemistry, Faculty of Sains and Technology, Airlangga University, Surabaya, INDONESIA.*

[3]*Department of Pharmaceutical Sciences, Faculty of Pharmacy, Airlangga University, Surabaya, INDONESIA.*

[4]*Department of Pharmaceutical Sciences, Hemvati Nandan Bahuguna Garhwal University (HNBGU) Srinagar Garhwal, Uttarakhand State, INDIA.*

Correspondence

Retno Widyowati

Department of Pharmaceutical Sciences, Faculty of Pharmacy, Airlangga University, Surabaya, INDONESIA.

E-mail: rr-retno-w@ff.unair.ac.id

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INTRODUCTION

Osteoarthritis, commonly known as degenerative joint disease, is one of the most prevalent forms of arthritis.[1] This disease is characterized by increasing cartilage degeneration and the development of osteophytes.[2] This joint injury is the result of an imbalance between anabolic and catabolic processes induced by chondrocytes.[3] In 2019, the prevalence of osteoarthritis was 527.81 million cases, an increase of 113.25 percent from the prevalence of 247.51 million cases in 1990.[4]

Joint chondrocytes are incapable of regulating production and degradation. This increases the production of pro-inflammatory cytokines such as Interleukin-1β (IL-1β) and Tumor Necrosis Factor-α (TNF-α) by chondrocytes. Increased IL-1β can cause chondrocytes to produce matrix metalloproteinases (MMPs) and disintegrin-like as well as thrombospondin-motif metalloproteinases (ADAMTs) this enzyme degrades substances.[5] The release of IL-1β influences the degradation of cartilage *via* the mechanism of releasing arachidonic acid and inducing the expression of cyclooxygenase-2 (COX-2) to boost prostaglandin E2 synthesis (PGE2).[6] The suppression of IL-1β is therefore anticipated to diminish the production of pro-inflammatory cytokines and to prevent the creation of various degrading proteins, such as MMP and ADAMTS.

Arcangelisia flava (L.) Merr. is a member of the *Menispermaceae* family these species are generally common from China to New Guinea in South-East Asia. This plant is a plant native to Borneo and has unique bright yellow wood color. Some local its name in Indonesia are kikoneng (West Java)[7] and kayo kuning (Palembang). It has traditionally been used to treat fever, diarrhea, hepatitis, worm infections, gastrointestinal disorders, and thrush. Dayak Ot Danum tribe in Kalimantan, specifically Tumbang Payang, uses the roots and stems of the plant to treat jaundice/hepatitis and liver diseases.

Saponins, flavonoids, and tannins are among the chemical compound of *Arcangelisia flava* (L.) Merr. This plant's leaf also includes alkaloids, flavonoids, terpenoids, and saponins.[8] The roots contain isoquinoline group alkaloids such as berberine, Jatrorrhizine, and palmatin. Other minor alkaloids include columbamine, dehydrokoridalmin, homoaromolin, and talifendin.[9] The most common bioactive compound is berberine, it is used as an antibacterial treatment by decreasing bacterial protein and cell wall synthesis,[10] an anti-inflammatory agent by inhibiting iNOS,[11] an antimalarial agent,[12] and an anticancer agent against MCF-7 (breast adenocarcinoma) and EGFR-2 (HER2-Positive) breast cancer line.[13] Pachybasin also possesses antimicrobial properties.[14] Jatrorrhizine is chemical compound that has been predicted to be able block bacterial metabolites, and its mechanism of columbamine, fibraurin, and palmatine has two-fold action as an antibacterial agent that might limit bacterial protein production.[10] *Palmatine also* reduced hepatotoxicity by inhibition of oxidative stress and apoptosis, and TUNNEL with decrease in plasma aspartate transaminase (AST), alanine transaminase (ALT), hepatic malondialdehyde, apoptosis and increase in hepatic glutathione.[15]

Several analytical techniques including infrared spectroscopy (IR), liquid chromatography-mass

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spectrometry (LC-MS), and gas chromatography (GC) with or without mass spectrometry (MS) are used to assess the phytochemical compound identification of herbal products.[16] In addition, the integration of analytical methods with *in-silico* tools and public web servers is commonly utilized to predict the inhibitory activity of a variety of phytochemical compounds against disease-related enzymes and target proteins.[17]

This research aims to assess the potential of *Arcangelisia flava* (L.) Merr as an anti-osteoarthritis agent. In this instance, LC-MS/MS analysis was performed to explain what compounds were present in the 70% ethanol extract of *Arcangelisia flava* (L.) Merr, and then the compounds analyzed LC-MS/MS will be used as a ligand compound in molecular docking to investigate the binding affinity of these phytochemical constituents to the target protein Interleukin-1β (PDB ID: 1ITB).

MATERIAL AND METHODS

Plant material and sample preparation

Arcangelisia flava (L.) Merr stems were collected from Soren Village, Kota Besi Subdistrict, East Kotawaringin district, Central Kalimantan, Indonesia. Its determination was carried out at UPT Herbal Laboratory of Materia Medica Batu. Fresh stems of this plant were sorted, cleaned, sliced thinly, and air-dried. Then, they were crushed with a grinder (Fomag FCT-Z200) to obtain a fine, bright yellow powder. The extraction procedure for this plant begins with weighing the grinding powder, followed by three days of maceration with 70% ethanol solvent at a ratio of 1:10. The filtrate was then separated through filtration, and the residue was twice macerated. All filtrate was collected and evaporated using a rotary evaporator (Buchi).

LC-MS/MS analysis

In the TLC method, chromatograms containing polar chemicals would appear first, followed by those containing less polar molecules. The QToF-MS detector (Xevo G2-S QTof, Waters, USA) was used to read the separation results to create a chromatogram peak. The LC-MS/MS equipment was utilized to determine the compounds found in the *Arcangelisia flava* (L.) Merr stems. The sample will be injected into the LC with a 5 µl microsyringe and inserted four times into the UPLC (LC: ACQUITY UPLC® H-Class System, Waters, USA) column ACQUITY UPLC BEH (Ethylene Bridge Hybride) C18 (1.8 µm 2.1 x 50 mm; Waters, USA). Liquid samples would be transformed into droplets and passed through a needle with a positive (+) ESI charge, 50–1200 m/z mass range with source and desolvation temperatures of 100 and 350°C, respectively. In addition, conical gas flow rates of 0 L/h and desolvation gas flow rates of 793 L/h were utilized in conjunction with impact energy ranging from 4 to 60 eV. Furthermore, the Q-ToF analyzer separated the ions produced by the detector. Solvent (A) water: formic acid and (B) acetonitrile: formic acid eluents with a flow rate of 0.2 ml/min were utilized in a gradient elution system. The chromatogram peaks were interpreted using the MestReNova application for data acquisition and analysis.

In-Silico studies

Instrument *In-Silico* studies

Hardware used was Legion 5 Pro 16AC6H laptop with 16.0 gigabytes of RAM, an AMD Ryzen 7 5800H processor, Radeon graphics at 3.20 GHz, an NVIDIA GeForce RTX 3060 graphics card, and the Microsoft® Windows® 10 Pro operating system. The laptop was linked to an online network (Wifi). Software Windows 10 pro-64-bit operating system, Discovery Studio Visualizer®, AutoDock Tools® 1.5.6 (The Scripps Research Institute, America), AutoDock 4.2.6 (The Scripps Research Institute, America), Autogrid 4.2.6 (The Scripps Research Institute, America), PyMOL® (DeLano Scientific LLC, Italy), Open Babel®, Marvin Sketch® (ChemAxon), Notepad++, LigPlot+ as well as the Protein Data Bank site, PubChem site.

Protein and ligand

Three-dimensional structure of the Type-1 Interleukin-1 Receptor Complexed with Interleukin-1 Beta protein (PDB ID: 1ITB) downloaded from the Protein Data Bank on the website https://www.rcsb.org/. While the reference compounds and ligand compounds or test compounds were received from LC-MS/MS data and downloaded from the website https://pubchem.ncbi.nih.gov/ in the (.sdf) format, structure preparation was performed using Marvin Sketch 20.21 (https://chemaxon.com).

Molecular docking studies

The crystal structures of Type-1 Interleukin-1 Receptor Complexed with Interleukin-1 Beta protein (PDB ID: 1ITB) downloaded from the Protein Data Bank. All water molecules were eliminated, missing residues and hydrogen atoms were added, and constrained energy minimization using the MMFF94 force field was used to construct a structurally stable structure for the ligand, whereas GROMOS96 was used for the protein. The grid box size was set to 0.375 A point distance and 60 x 60 x 60 pixels. The grid box's coordinates were x=48.729; y=3.25, and z=16.546.[18]

The semi-flexible docking method involves establishing the ligand in a flexible manner while the protein's shape remains stiff. The Lamarckian Genetic Algorithm was used to perform molecular docking with a population size of 150 individuals and a maximum eval number of 2,500,000 for every 100 independent runs. The optimal pose was determined based on the lowest binding energy score (ΔG) with inhibition constant (Ki) value and the functional essential amino acid, which Discovery Studio Visualizer identified as playing a part in docking interaction.

RESULT AND DISCUSSION

LC-MS/MS analysis

In this research, phytochemical compounds in *Arcangelesia flava* (L.) Merr were detected using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). Therefore, the created method of a triple quadrupole detector was utilized in this investigation. Due to its great selectivity and sensitivity, this technique is regarded as more efficient than other LC techniques. This metabolomic analysis manifested the presence of alkaloid, flavonoid, furano-diterpene, hydroxyquinoline, phenylpropanoid, phenol, and fatty acid. This result presented in (Table 1) and the Total Ion Chromatogram (TIC) of *Arcangelesia flava* (L.) Merr extract is presented in (Figure 1).

(Table 1) showed that peaks at retention time (Rt) 6.596 is protoberberine compounds. It is supported by research conducted by Verpoorte *et al.* (1982) where the bioactive compound in *Arcangelisia flava* (L.) Merr is berberine.[33] Because of their wide variety of biochemical and pharmacological effects, they have potential in different therapeutic areas such as cancer, inflammation, diabetes, depression, hypertension, and various infectious regions. These alkaloids have garnered substantial attention over the past decade.[34] Other protoberberine compounds were discovered included jatrorrhizine with a retention time of 6,153 and palmatine with a retention time of 9.957. This result is consistent with research conducted by Yu (2014).[35] Isopycnarrhine (Rt of 1.282), pycnarrhine (Rt of 2.462), and fibleucin (Rt of 5.379) are furano-diterpene compounds that were identified from the *Arcangelisia flava* (L.) Merr. These furano-diterpenes are bicyclic diterpenoids whose molecular skeletons are composed of four isoprene units, and the majority of these diterpenes have an ester ring or an oxygen ring, which is also a fascinating phenomenon observed in the *Arcangelisia*

genus. Phenylpropanoid, phenol, and fatty acid compounds such as sinapic acid, sinapaldehyde, docosanoic acid were also found in the 70% ethanol extract of *Arcangelisia flava* (L.) Merr.

Molecular docking

A total of 15 compounds obtained from the results of LC-MS/MS were then carried out by molecular docking of the interleukin-1 beta PDB protein ID: 1ITB. The binding interactions of the molecules have been determined based on their free energy values and the main role of amino acid interaction. The results of molecular docking can be seen in (Table 2).

Based on the docking results, several compounds from *Arcangelisia flava* (L.) Merr were detected which had the best conformation with the lowest energy. Their bioactive compound with the lowest free binding energy was 3-hydroxy-3',4',5'-trimethoxyflavone with (ΔG=-7.72 kcal/mol), followed by fissisaine (ΔG=-6.91 kcal/mol), and demethylene berberine (ΔG=-6.85 kcal/mol). However, when they compared to the positive control, the meloxicam's bond energy value was lower than the three highest compounds, namely -8.14 kcal/mol. High values of negative free binding energy (ΔG) imply spontaneous protein-ligand binding influences and stabilizes protein-ligand interaction. Additionally, they are a superior molecular docking prediction

Table 1: Spectral information of LC-MS/MS.

No	Retention Time	Molecular Weight (gr/mol)	Fragmentation (m/z)	Tentative Compound	Reference
1	1.282	192.17	148; 177; 192; 222; 223; 314; 328; 329	Isopycnarrhine ($C_{11}H_{14}NO_2$)	19
2	2.462	192.23	177; 192; 193; 194	Pycnarrhine ($C_{11}H_{14}NO^{2+}$)	19
3	3.039	224.21	192; 222; 223; 236	Sinapic acid ($C_{11}H_{12}O_5$)	20
4	3.742	208.21	190; 206; 207; 328	Sinapaldehyde ($C_{11}H_{12}O_4$)	21
5	3.960	327.40	192; 204; 328; 329; 330	Pallidinine ($C_{19}H_{21}NO_4$)	22
6	4.571	328.30	207; 328; 329; 342	3-hydroxy-3',4',5'-trimethoxyflavone ($C_{18}H_{16}O_6$)	23
7	5.211	324.10	208; 309; 324; 356; 357; 358	Demethyleneberberine ($C_{19}H_{18}NO_4$)	24
8	5.450	324.12	208; 309; 324; 325; 328; 536	Stepharanine ($C_{19}H_{18}NO_4$)	25
9	5.739	356.40	192; 352; 356; 357; 370	Fibleucin ($C_{20}H_{20}O_6$)	26
10	6.153	338.40	322; 323; 338; 339; 340	Jatrorrhizine ($C_{20}H_{20}NO^{4+}$)	27
11	6.596	336.40	278; 320; 336; 337; 338	Berberine ($C_{20}H_{18}NO^{4+}$)	28
12	8.860	340.60	330; 336; 340; 341; 378	Docosanoic acid ($C_{22}H_{44}O_2$)	29
13	9.584	370.50	336; 338; 342; 370; 408; 680; 681	N-methyltetrahydropalmatine($C_{24}H_{28}NO^{4+}$)	30
14	9.781	354.31	338; 336; 354; 355; 392; 492; 729	Fissisaine ($C_{16}H_{18}O_9$)	31
15	9.957	352,30	322; 336; 352; 353; 354	Palmatine ($C_{21}H_{22}NO^{4+}$)	32

Table 2: The docking result of compounds from LC-MS/MS against 1ITB.

No	Compound	Free Binding Energy (ΔG)	Inhibition Constant (Ki)
1	Meloxicam	-8.14	1.07 Micromolar
2	3-hydroxy-3',4',5'-trimethoxyflavone	-7.72	2.21 Micromolar
3	Fissisaine	-6.91	8.68 Micromolar
4	Demethyleneberberine	-6.85	9.49 Micromolar
5	Jatrorrhizine	-6.66	13.12 Micromolar
6	Pycnarrhine	-6.44	19.13 Micromolar
7	Fibleucin	-6.39	20.77 Micromolar
8	Berberine	-6.10	34.00 Micromolar
9	Stepharanine	-5.97	42.06 Micromolar
10	Isopycnarrhine	-5.83	53.46 Micromolar
11	Palmatine	-5.74	61.77 Micromolar
12	Sinapic acid	-5.58	81.24 Micromolar
13	N-methyltetrahydropalmatine	-5.38	113.59 Micromolar
14	Pallidinine	-5.38	113.67 Micromolar
15	Sinapaldehyde	-5.17	161.26 Micromolar
16	Docosanoic acid	-4.75	327.93 Micromolar

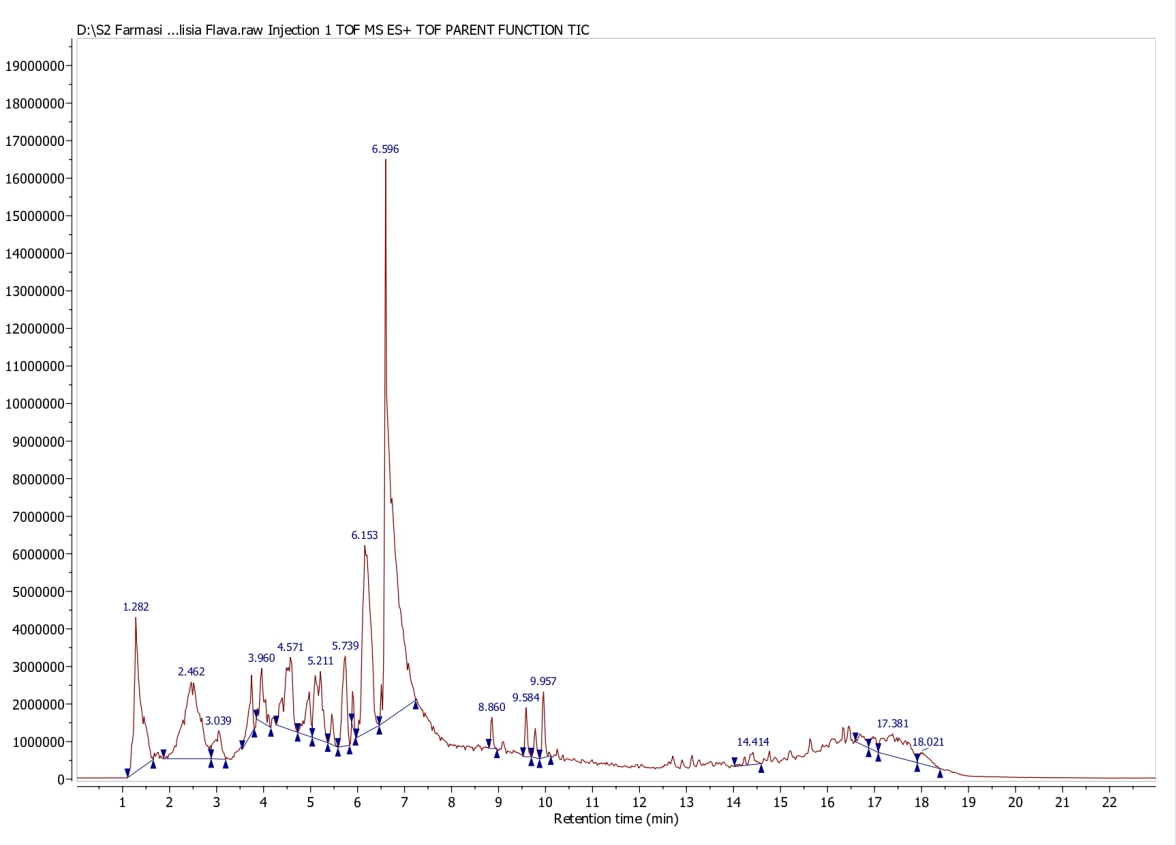

Figure 1: Total Ion Chromatogram of *Arcangelisia flava* (L.) Merr extract using LC-MS/MS

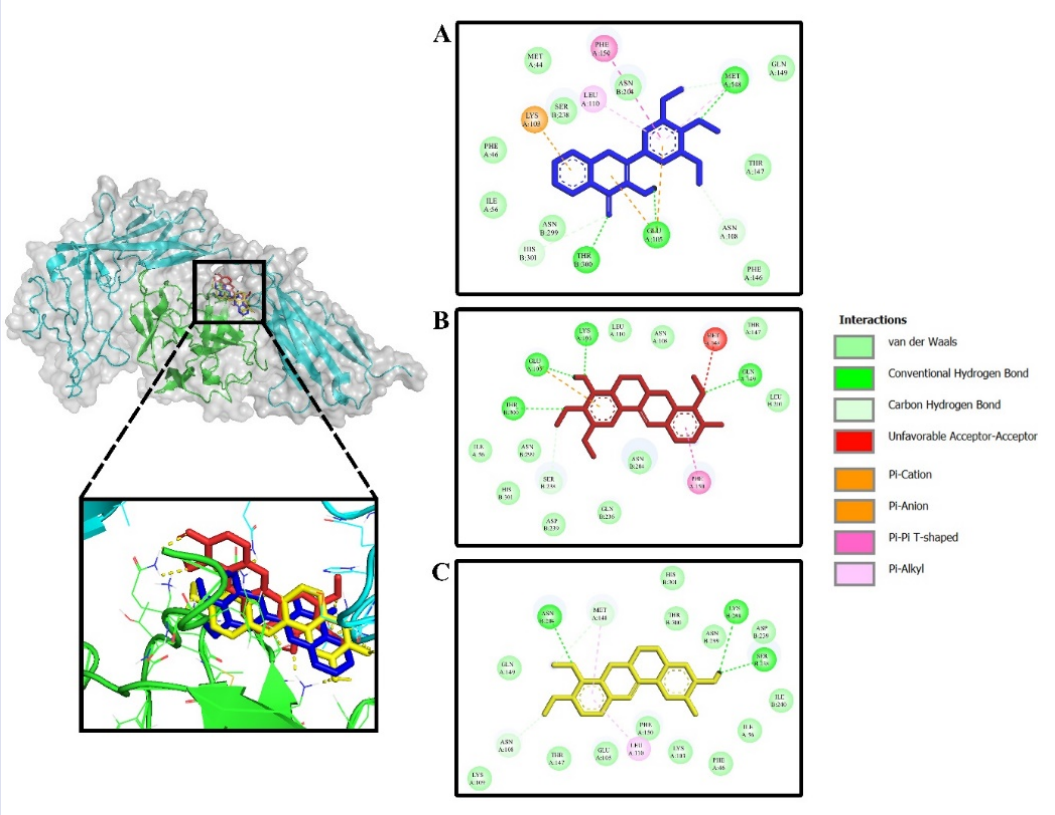

Figure 2: Protein-Ligand interaction of top three best docking result (A) 3-hydroxy-3',4',5'-trimethoxyflavone (B) Fissisaine (C) Demethyleneberberine

inhibitor.[36] The lowest binding score correlated with the lowest inhibition constant (Ki) value.

The 3-hydroxy-3',4',5'-trimethoxyflavone is an alkaloid compound that has anti-inflammatory, antibacterial, and antifungal activities against *Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus faecalis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, *Candida krusei,* and *Candida galabrata*. It also shows moderate antitrypanosomal activity with a MIC value of 19.0 ug/ml. The 5-hydroxy-3',4',7-trimethoxyflavone shows prominent inhibitory activity against soybean lipoxygenase, and it can significantly inhibit nitric oxide production, and induce a reduction in the mRNA expressions of inducible nitric oxide synthase, as well as cyclooxygenase-2 in lipopolysaccharide-induced inflammation in RAW 264.7 macrophages targeting a reduction in prostaglandin-E2 level. This compound also inhibits the production of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β.[37-39]

The fissisaine has not been studied as active against the interleukin-1β receptor. However, it is protoberberine alkaloid because its structure is similar to other protoberberine compounds such as berberine. Therefore, it may have the same activity as other protoberberine such as lowered pro-inflammatory cytokines, specifically IL-1 β, IL-6, IL-8, and TNF-α.[40] According to research conducted by Thuy (2006), this compound was isolated from *Stephania rotundifolia* Lour.[41] It is a member of the menispermaceae group and widespread throughout Asia. It can be used to treat fever, stomach complaints, disorders of the urinary system, diarrhea, and gastrointestinal tract.

Demethylene berberine has been reported to possess multiple pharmacological activities, especially anti-inflammation and immunoregulation. It inhibited mitochondrial production and maintained mitochondrial homeostasis during an inflammatory reaction. In addition, it also inhibited the maturation of IL-1β in a mitochondria-dependent way.[42] This compound also dramatically mitigated weight loss and decreased myeloperoxidase (MPO) activity, while reducing the production of pro-inflammatory cytokines such as interleukin IL-6 and tumor necrosis factor-a (TNF-α) and inhibiting the activation of the NF-kB signaling pathway and interferon (IFN)-γ. ROS production and pro-inflammation cytokines were markedly inhibited by demethylene berberine.[43]

Based on a molecular docking research, the top three compounds with the highest docking score, namely 3-hydroxy-3',4',5'-trimethoxyflavone, fissisaine, and demethyleneberberine, have relatively higher chemical potential as interleukin-1 inhibitors. Based on prior wet and dry lab investigations, they also exhibit anti-inflammatory properties.

The interaction of amino acid residues from the results of molecular docking can be seen in (Figure 2), This result tries to discover essential amino acids that contribute to the hydrogen-active site interleukin-1β interaction, such as LYS103, GLU105, SER238, THR300, ASN204, MET148, PHE146, ASN108, GLN149, GLU265, LEU237, LYS270, and ARG4. The hydrogen bond is one of the non-covalent binders that play an important role in docking score, complex formation, and binding mode strength.[44] In this study, the amino acid with the largest role in this molecular docking is MET148, LYS 103, and THR300. According to previous research, Site A of the IL-1β protein (PDB ID: 1ITB) consists of the residues 11, 13-15, 20-22, 27, 29-36, 38, 126-131, 147, and 149. The residues numbered 1-4, 6, 46, 48, 51, 53-54, 56, 92-94, 103, 105, 106, 108, 109, 150, and 152 make up site B. The two hydrophilic and hydrophobic residues are ARG4, GLN48, GLU51, ASN53, LYS93, GLU105, and ASN108[18]. The amino acid residues which are produced by the three compounds with the highest docking scores have amino acid residues that are consistent with past research.

Hydrogen bonds play a role in this interaction, and the surface of the binding site (site A) features a pocket to accommodate the IL-1 side chain. Therefore, apart from the hydrogen bonds, an important component of the binding energy of these sites likely originates from the van der Waals contacts between IL-1β and IL-1R.

According to the findings of this study, some of these amino acids create hydrogen bonds that are responsible for the energy binding score and also serve to stabilize the IL-1β inhibitor ligand protein. These results demonstrate that the ligand docking position on IL-1β is optimal for the active site containing the catalytic region of the enzyme, which in osteoarthritis functions as an inhibitor of the synthesis of degrading proteins.

CONCLUSION

The 70% ethanol extract of *Arcangelisia flava* (L.) Merr from LC-MS/MS analysis results indicated that this extract contains 15 components, including alkaloids, flavonoids, furano-diterpene, hydroxyquinoline, phenylpropanoids, phenols, and fatty acids. The hydroxy-3',4',5'-trimethoxyflavone received the highest molecular docking score in the *in-silico* molecular docking test, followed by fissisaine and demethylene berberine. This information is helpful for future bioassay investigations of their potential application as a novel osteoarthritis treatment. It will be necessary to isolate the molecules obtained from docking explained in the present study.

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CONFLICTS OF INTEREST

The authors declared no conflicts of interest.

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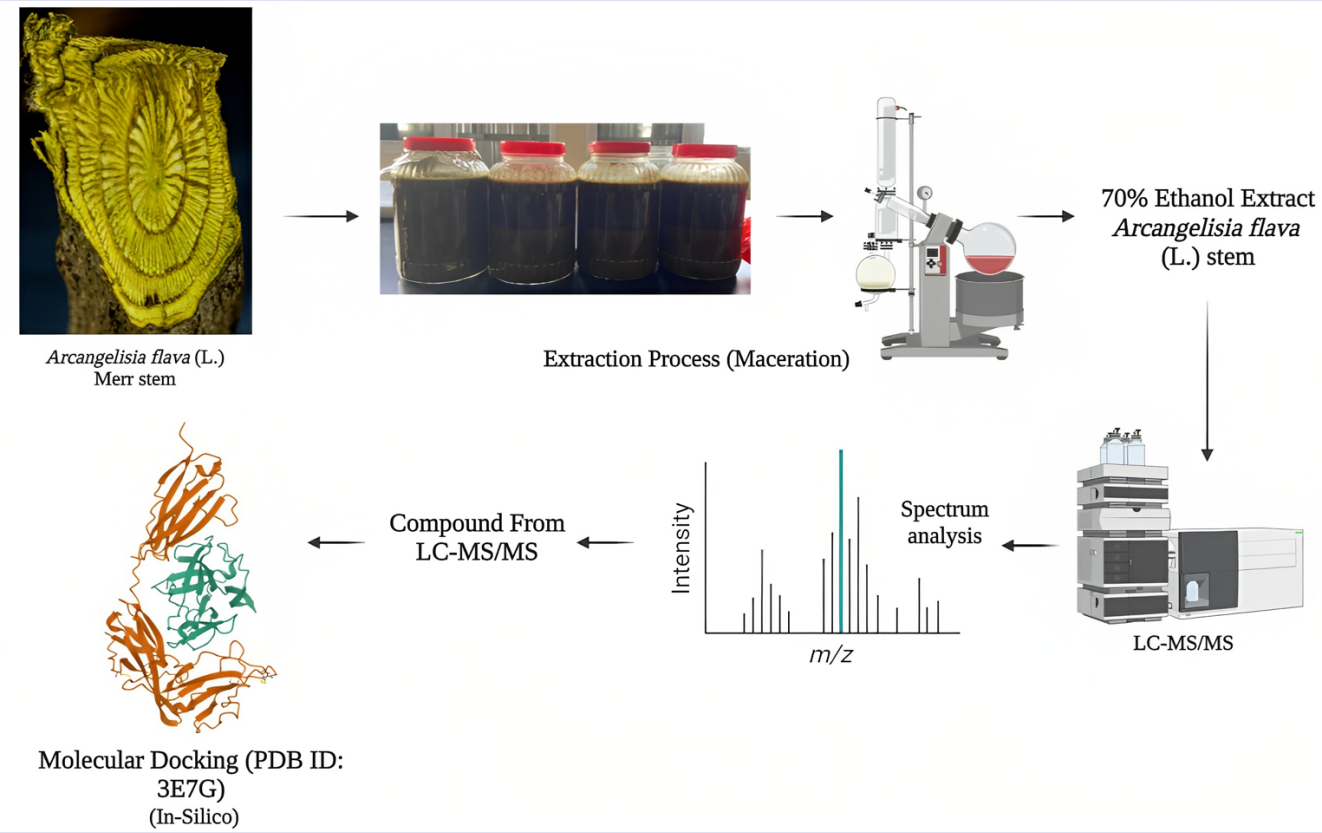
GRAPHICAL ABSTRACT



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