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Dwi Anita Suryandari
Department of Biology, Faculty of Medicine, Universitas Indonesia, Indonesia, dwi.anita@ui.ac.id

Puji Sari
Department of Biology, Faculty of Medicine, Universitas Indonesia, Indonesia, Puji.Sari@gmail.com

Hadi Sunaryo
Department of Pharmacy, Faculty of Pharmacy and Science, Universitas Muhammadiyah Prof. DR. Hamka, Indonesia, hadi_sunaryo@uhamka.ac.id

Khaerunissa Anbar Istiadi
Biology Study Programme, Faculty of Science, Institut Teknologi Sumatera, Indonesia, khaerunissa.istiadi@bi.itera.ac.id

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Article

A Computational Exploration: Docking Analysis of Compounds from *Foeniculum vulgare* as Potential Aromatase Inhibitors for Endometriosis Candidate Therapy

Dwi Anita Suryandari [1], Puji Sari [1], Hadi Sunaryo [2], Khaerunissa Anbar Istiadi [3*]

[1] Department of Biology, Faculty of Medicine, Universitas Indonesia, Jakarta 10430, Indonesia
[2] Department of Pharmacy, Faculty of Pharmacy and Science, Universitas Muhammadiyah Prof. DR. Hamka, Jakarta 13460, Indonesia
[3] Biology Study Programme, Faculty of Science, Institut Teknologi Sumatera, Lampung 35365, Indonesia
* Correspondence: khaerunissa.istiadi@bi.itera.ac.id

Abstract: Aromatase inhibitors (AI) drugs commonly used for controlling symptoms and size of endometriotic implants, making them a promising second-line therapy for endometriosis treatment. Pretreatment with letrozole, an AI, combined with leuprolide acetate and resveratrol, has been found to improve in vitro fertilization (IVF) outcomes in women with mild endometriosis. These compounds can be extracted from plants such as *Foeniculum vulgare*. In this study, we screened and conducted analysis of ten phenolic compounds from *Foeniculum vulgare* using molecular docking with Mcole server. Results showed that three phenolic compounds: trans-resveratrol (TR), kaempferol coumaril (CC), have low gibbs energy compared with resveratrol (R). The binding modalities of compound TR and compound R were hydrogen-bonding between the hydroxyl and oxygen atom and Thr310 and hydrophobic interactions with Phe187, Ala272, Asp275, Ala189 and compound R exhibited cation-π interactions between Val336 as binding activity from aromatase. Aromatase inhibitors and resveratrol from *Foeniculum vulgare* has potential to modulate hormonal pathways, including aromatase inhibition.

Keywords: Aromatase; *Foeniculum vulgare*; molecular docking; endometriosis

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1. Introduction

In comparison to the rates of endometriosis that are found on other continents, the incidence rate of this condition is significantly higher among women in Asia. Only a small amount of information is currently known regarding the epidemiology of endometriosis in East Asian populations; therefore, additional research is required to enhance the management of this disease [1]. Endometriosis impact the quality of life and fertility. Genetic and environmental variables play a role when it comes to the presentation and progression of endometriosis. Additionally, there are disparities in the risk factors and treatment responses between populations of Asian and European-American descent [2]. Endometriosis is frequently misdiagnosed and underrecognized by clinicians, particularly in individuals who are experiencing asymptomatic infertility that any other factor cannot explain.

The dysregulation of several different molecular pathways is a component of the pathophysiology of endometriosis [3]. These mechanisms include abnormalities in aromatase expression, steroidogenic factor 1, and estrogen receptors. Understanding these mechanisms is essential for developing treatments that help treat endometriosis. Targeting oxidative stress, inflammation, hormonal abnormalities using aromatase inhibitors

(AI), and immunological dysregulation are all potential treatment techniques that could be utilized. Additional study is required to investigate these pathways and develop medicines specifically targeted for endometriosis. In many locations throughout the human body, the aromatase enzyme, a product of the CYP19A1 gene, is responsible for catalyzing the conversion of androgens to estrogens [4]. The production of estrogens significantly contributes to the development of neoplastic cells, particularly in women's health [5]. Aromatase inhibitors (AI) have demonstrated a high level of clinical success in the management of endometriotic symptoms and the size of endometriotic implants, which positions them as a potentially useful second-line medication for the treatment of endometriosis [6]. They have shown remarkable clinical, radiographic, and endoscopic responses in patients of deep infiltrative endometriosis who have been recalcitrant to treatment [7]. Aromatase inhibitor (AI) has developed as a novel class of medications that can provide clinical relief and fertility treatment for endometriosis. It has been discovered that they are beneficial in treating pain symptoms and infertility that are linked with endometriosis, with efficacy that is comparable to that of other medical therapy modalities [8]. AIs are a novel class of medications that have emerged as a potential treatment for endometriosis, with the potential to alleviate symptoms and improve fertility. In addition, it has been discovered that pre-treatment with the artificial insemination drug letrozole, in conjunction with leuprolide acetate and resveratrol, can improve the outcomes of in vitro fertilization (IVF) in women who have slight or moderate endometriosis. Aromatase inhibitors (AI) that are derived from natural products have been given clinical consideration for the treatment of post-menopausal breast cancer and have the potential to act as chemopreventive agents [9].

As an additional point of interest, a sizeable number of the patients are diagnosed at an advanced stage, which necessitates chemotherapy after surgery. However, there are certain individuals who are unable to tolerate chemotherapy. Therefore, efforts are required to find alternative treatments.

Foeniculum vulgare, known as "adas" in Indonesia, is one of medicinal plants that has high antioxidant activity due to its phenolic compounds [10,11,12]. Anti-aromatase pharmaceuticals extracted from *Foeniculum vulgare* can be used for the treatment of benign prostate hypertrophy and breast cancer [13,14]. Studies showed that *Foeniculum vulgare* has theraupetic effects in management of menopausal symptoms [15], management of women's health [16], PCOS treatment, and dysmenorroea [17]. This study aim to analyze compounds from Fennel root extract *Foeniculum vulgare* (Fennel) as aromatase inhibitors potential candidate for endometriosis treatment by molecular docking approach

2. Results and Discussion

2.1 Preparation of Foeniculum vulgare compounds

The compounds from fennel were characterised as flavonoids and phenolic compounds. Structures of several compounds in *Foeniculum vulgare* shown at Figure 1. In another study, the chemical active substances from water and ethanol extracts of F.*vulgare* seeds have been reported have antioxidant activity [10,11,12].

Aromatase, a CYP enzyme that is a monooxygenase, was involved in the process of converting androgens (C19) to estrogens (C18) by the demethylation and aromatization of the steroidal A-ring. It is encoded by the gene CYP19, which is located in chromosome 15q21 [18]. Aromatase are responsible for a wide variety of physiological processes, including homoeostasis of glucose and lipids, brain function, follicular growth, bone mineralization, epiphyseal closure, and coordination of the ovulatory process. Figure 2 depicts the three-dimensional structure of aromatase, and Figure 3 presents the sequence annotation of aromatic compounds.

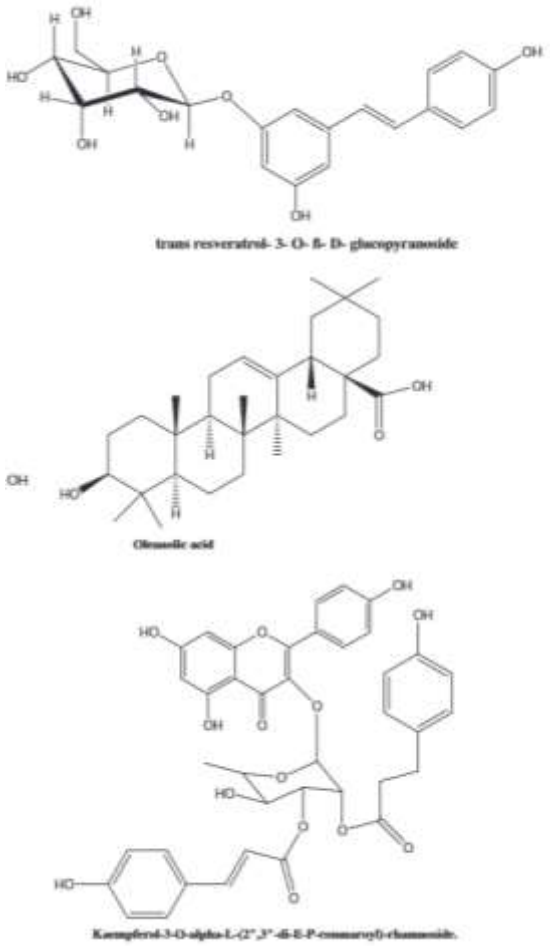

Figure 1. Chemical active from Foeniculum vulgare as aromatase inhibitor

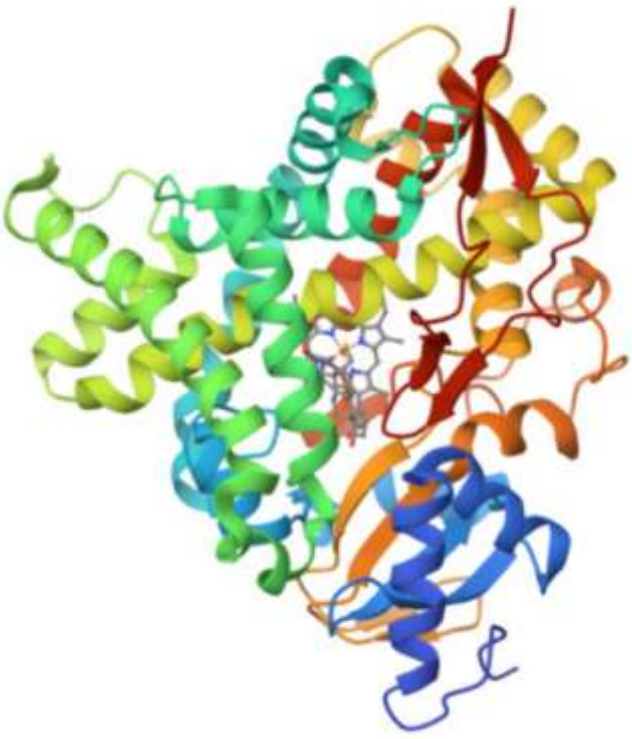

Figure 2. 3D structure Human Cytochrome P450 Aromatase

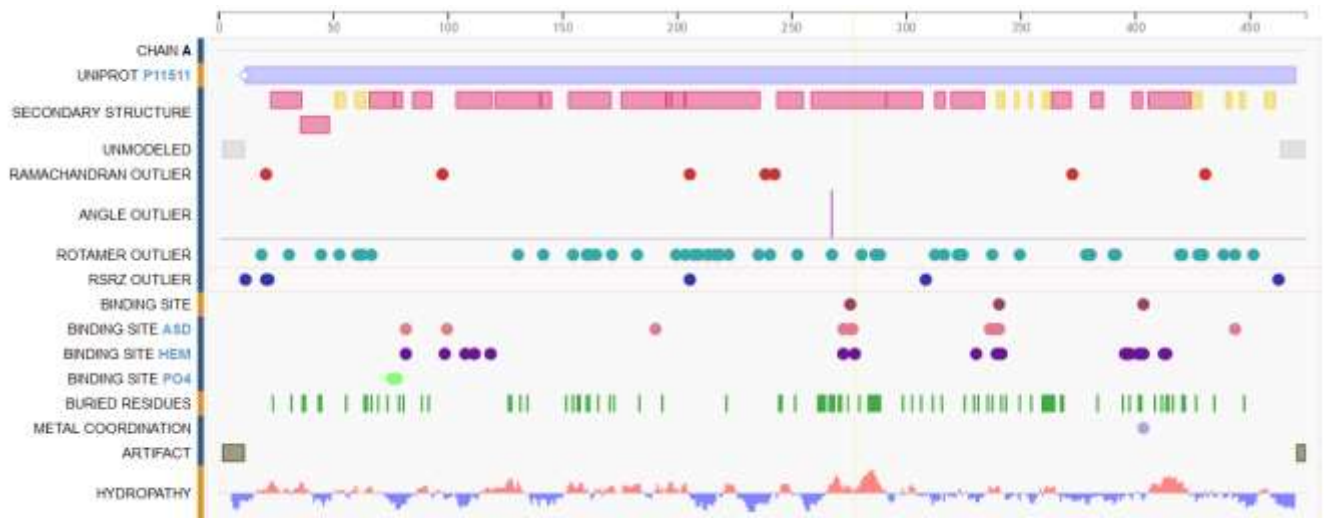

Figure 3. Sequence Annotations 3D structure of Cytochrome P450 Aromatase

2.2 Molecular Docking

Molecular docking is drug discovery method which investigating the interaction and recognition that occurs between receptors and ligands. The study of intermolecular interactions and the prediction of their binding patterns and affinity are the primary activities of this theoretical simulation technique, which focuses on the research of these interactions. Molecular docking has emerged as a significant technology in the field of computer-aided drug development during the past several years. The data that were obtained using the molecular docking program are presented there in Table 1. As a result of the processing carried out by Mcule.com, the complexes that have the best docking of the receptor and ligand are displayed.

Table 1. Gibbs Energy of aromatase with ligand from *Foeniculum vulgar*

Molecule	Gibbs energy (kkal/mol)	H interaction
3-caffeoylquinic acid	-6.023	Gly185, Ala189
4-caffeoylquinic acid	-5.921	Ala189
kaempferol-3-O-glucoside	-6.792	Phe187, Val279, Ile72
kaempferol-3-O-rutinoside	-6.533	Ile72, Leu445
quercetin-3-O-galactoside	-6.210	Asp118, Ala189
eriodictyol-7-rutinoside	-5.921	Phe187, Val279
Kaempferol-3-O-alpha-L-(2",3"-di-E-P-coumaroyl)-rhamnoside	**-8.087**	**Phe187, Ala272, Asp275, Ala189**
1,5-O-dicaffeoylquinic acid	-5.732	Gly185, Ala272
trans resveratrol- 3- O- ß- D-glucopyranoside (TR)	**-8.736**	**Phe187, Ala272, Asp275, Thr276**
rosmarinic acid	-5.779	Leu445
Resveratrol (R)	**-8.082**	**Asp118, Phe187, Ala272, Asp275, Val336**

In general, it is generally considered that the binding capacity is stronger when the docking binding free energy is lower than -8.376 kcal/mol. The binding energies of the three active components to the top three ranked were all less than -8 kcal/mol, as demonstrated in Table 1. This indicates that there is a significant affinity between resveratrol as opposed to the other two active ingredients. A lower or more negative bond energy value indicates a stronger interaction between the ligand and protein. A smaller bond energy value indicates that the tendency to interact spontaneously between the ligand-receptor is higher [19,20]. The strength of the interaction between the compound and the protein is due to the stability and strength of the non-covalent interaction between the test compound and the target protein.

The binding interaction of compound TR and compound R were hydrogen-bonding between the hydroxyl and oxygen atom and Thr310 and hydrophobic interactions with Phe187, Ala272, Asp275, Ala189. In addition, compound R exhibited cation-π interactions between Val336 as binding activity from aromatase.

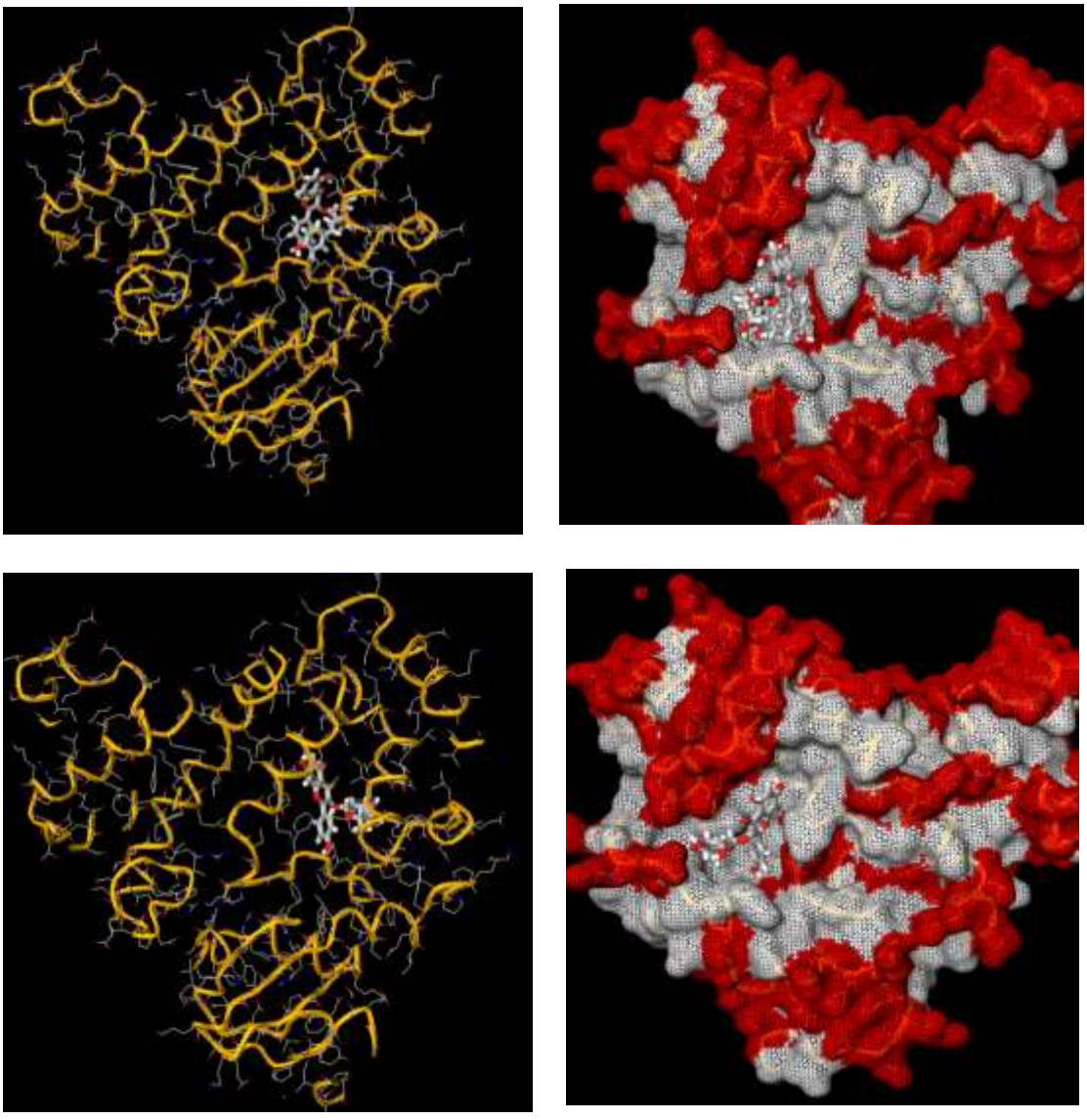

Figure 4. Complex of molecular docking of aromatase A1. 3D Aromatase with trans resveratrol- 3- O- ß- D- glucopyranoside A2. molecular surface complex Aromatase with trans resveratrol- 3- O- ß- D- glucopyranoside. B1. 3D Aromatase with resveratrol A2. molecular surface complex Aromatase with resveratrol

Inhibitors of aromatase are substances that prevent the enzyme aromatase from performing its function. Aromatase is the enzyme that is accountable for the

transformation of androgens, which are male hormones, into estrogens, which are feminine hormones. In the therapy of hormone-dependent ailments like breast cancer and, perhaps, in the setting of hormone-related disorders like endometriosis, these inhibitors are frequently utilized. Breast cancer is one kind of condition that is dependent on hormones.

Resveratrol, on the other hand, is a naturally occurring polyphenol that may be discovered in a variety of plants, such as peanuts and red grapes. The potential health benefits that it may offer, such as anti-inflammatory and antioxidant characteristics, have brought it to the attention of several people. The possibility of resveratrol to act as a natural aromatase inhibitor has been the subject of investigation in several research that have addressed the function that resveratrol plays in the modulation of hormonal pathways. The activity of aromatase is inhibited by artificial intelligence due to its interaction with the substrate-binding site of aromatase, and based on their structure. For these reasons, the objective of various medicinal chemistry research groups that have synthesized novel steroidal artificially intelligent substances (AIs), non-steroidal AIs, or investigated the effect of natural products like resveratrol is to reduce the adverse effects and improve the clinical efficacy of the drug [21].

Resveratrol is a naturally occurring polyphenol that can be found in a wide variety of foods, such as grapes and plantain (*Foeniculum vulgare*). In a variety of biological processes, the nonflavonoid polyphenol possesses its antioxidant, anti-inflammatory, and neuroprotective capabilities, which means that it has the potential to be involved in the treatment of a variety of disorders [22].

Recent research has shown that this particular polyphenol plays a role in all three stages of the cancer process: carcinogenesis, tumor development, and organ metastasis [23,24]. The findings of these research have provided some hints that can be used to determine whether or not there is a connection between resveratrol and type I endometrial cancer. Molecular docking is used in our research to find resveratrol and its potential targets. The purpose of this research is to investigate the probable processes that underlie the effects of resveratrol on type I endometrial cancer.

The difference between aromatase inhibitors and resveratrol derived from fennel rests in the fact that resveratrol has the ability to alter hormonal pathways, including aromatase inhibition. On the other hand, additional research is required to understand the particular mechanisms, ideal dosages, and potential therapeutic applications in disorders such as endometriosis. Before beginning any new treatment or supplement regimen, it is imperative to always seek the advice of qualified medical professionals.

4. Materials and Methods

Aromatase as protein target were retrieved from Protein Database (PDB) (https://www.rcsb.org/) with protein ID 4KQ8. Protein were downloaded in PDB format. Protein preparation was conducted by separating protein with native ligand and non-protein molecules by PyMOL software.

Compounds used for this study were retrieved from *Foeniculum vulgare* GCMS result. Compounds used are 3-caffeoylquinic acid, 4-caffeoylquinic acid, kaempferol-3-O gluco-side, kaempferol-3-O-rutinoside, quercetin-3-O-galactoside, eriodictyol-7 rutinoside, Kaempferol-3-O-alpha-L-(2",3"-di-E-P-coumaroyl)-rhamnoside, 1,5-O-dicaffeoylquinic acid, trans resveratrol- 3- O- ß- D- glucopyranoside (TR), rosmarinic acid. Resveratrol (R), compounds commonly used as estrogen blocker, was used as positive control in molecular docking. Using the ChemDraw software, the three-dimensional (3D) structures of the *Foeniculum vulgare* compounds were rendered after being retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). After that, these files were loaded into Mcule.com. Subsequently, the Mcule.com software was utilized once again to add hydrogen and compute the overall charges. It was determined that the research object would be the pose with the lowest energy by the use of the clustering tool on Mcule.com.

High-quality three-dimensional and two-dimensional structures of small molecules and proteins were generated by PyMOL.

Docking of compounds used as ligands towards the target protein was conducted with Mcule.com. Redocking was conducted on Aromatase Protein and its native ligand to determine the active site of protein. To ensure that the docking procedure was successful, the co-crystallized ligand, also known as AD, was re-docked into the aromatase protein structure binding pocket.

5. Conclusions

Aromatase inhibitors compounds (TR, CC) from *Foeniculum vulgare* has potential to modulate hormonal pathways, including aromatase inhibition.

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