cj976

by Capa Cj976

Submission date: 05-Oct-2018 02:38PM (UTC+0700)
Submission ID: 1014338083
File name: CJ976_PRS_3562_Bioinformatics_clean_version.doc (971K)
Word count: 4375
Character count: 26385

TABLE REPORT OF TRANSLATION AND PROOFREADING TEAM CAPA				
Plagiarism Detected	**Final Plagiarism (After Edit)**	**Language Improvisation**	**Status**	**Notes (ATTENTION)**

IN SILICO STUDY OF FATIMAH GRASS (*Anastatica hierochuntica* L) ESTROGENIC ACTIVITIES AND ITS POTENTIAL AS PHYTOESTROGENS

Heny Astutik[1], Budi Santoso[2], Mangestuti Agil[3]

1. Department of Midwifery, Health Polytechnic of Malang, East Java of Indonesia
2. Faculty of Medical, University of Airlangga, Surabaya, East Java of Indonesia
3. Department of Pharmacy, University of Airlangga, Surabaya, East Java of Indonesia

Corresponding author : Email : henyast21@gmail.com, Contact phone : +21825974866

ABSTRACT

Fatimah grass (*Anastatica hierochuntica* L.) is a desert plant known as a traditional Indonesian medicine to help the childbirth process become more comfortable; however, there is no scientific evidence to support this. Previous studies have reported that methanol and water extracts from these plants have antioxidant, antifungal and antimicrobial activity. Also, several studies based on *in vivo* analysis have shown that *Anastatica hierochuntica* L. has anti-inflammatory, anti-melanogenic and gastroprotective activity as well as hepatoprotective properties. *Anastatica hierochuntica* L. has been found to contain flavonoid substances such as luteolin-7-glucoside, isovitexin, kaempferol 7-glucoside, kaempferol 3 rhamnoglucoside, quercetin, rutin, and glucosinolates, i.e., glucoiberin, glucocheirolin, and sterols. Based on the content of these compounds, *Anastatica hierochuntica* L. is a phytoestrogen that can bind to estrogen receptors in the human body and produce a pro-estrogenic or anti-estrogenic effect on the target tissue. Thus, it may be used for herbal treatment. In silico tests were performed using computer simulation methods to initiate the discovery of new drug compounds or improve efficiency in the drug compound activity optimization. In silico tools can be used to predict, hypothesize and identify novel findings or new advances in the field of treatment and therapy. This study aimed to determine the prediction of estrogenic activity compounds in Fatimah grass (*Anastatica hierochuntica* L.) and its potential as a phytoestrogen with target agonists to the estrogen receptor using in silico tests. In silico studies were done using Pass Server and Molecular Docking by utilizing the role of computational chemistry and the ACD/I-Lab program online. In this study, it was found that active compounds in Fatimah grass have low activity against estrogen receptor agonists because the average value of activity obtained was low (<0.3). The results of molecular docking using the PyRx program showed that isopimaric acid was a compound that has a binding affinity value close to that of estradiol, so isopimaric acid is predicted to be a phytoestrogen.

Keywords: *Anastatica hierochuntica* L., Estrogenic Activity, In Silico, Phytoestrogens

INTRODUCTION

Herbaceous plants have been widely used in various countries as a traditional medicine for pregnant women to treat various pregnancy-related diseases thereby improving the health status of pregnant and postpartum mothers (Norden & Havnen 2005). One of the herbaceous plants known to facilitate childbirth is Fatimah Grass (*Anastatica hierochuntica* L.), a desert plant originating from Arabia. Empirically, the use of Fatimah grass in Indonesia for mothers who will give birth was often reported for pregnant women who believed that it could facilitate the process of uterine contractions during childbirth.

Previous studies showed that *Anastatica hierochuntica* L. extract contained phenolic compounds (51.97 mg/gd.w), flavonoids (42.53 to 46.28 mg/gd.w), β-carotene (2.27µg/g) and lycopene (2.43 µg/g) (Mohamed, et al. 2009). The flavonoid contents are luteolin-7-glucoside, isovitexin, kaempferol 7-glucoside, kaempferol 3 rhamnoglucoside, quercetin, rutin and glucosinolates such as glucoiberin and glucocheirolin as well as sterols. Rizk et al. (1993) explained that the lipid fraction of *Anastatica hierochuntica* plants was produced hydrocarbon isolation (especially: C25H52, C29H60 and C31H64) and the sterol fraction (β-sitosterol, campesterol, stigmasterol and cholesterol) also identified two flavonoids, namely luteolin and luteolin 7-0-glucoside.

Flavonoids have estrogenic activity and significantly increase the cytosolic ERα concentrations which also increase uterine sensitivity after binding to estrogen (Breinholt et al. 2000). Phytoestrogens or herbal estrogens can bind to estrogen receptors produced by the body and produce pro-estrogenic or anti-estrogenic effects on the target tissue. The response depends on the amount of estrogen and estrogen receptor produced. Several studies have successfully obtained an overview of the effects of phytoestrogens, including the ability to bind to estrogen receptors on target organs and also induce gene products that have a specific response to estrogen (Kuiper et al., 19[illegible]).

Its receptors mediate the mechanism of action of estrogen. Estrogen receptors (ER) are members of the nuclear receptor hormone superfamily, which includes nearly 150 members. Estrogen receptors bind to the hormone estrogen for the transcription process in specific genes, consisting of two isoform subtypes, namely ERα and ERβ. Estrogen bonding to receptor induces changes in receptor structures, leading to dimerization, pre-transcriptional modification, and binding to DNA enhancing elements in the promoters of specific genes that will interact with transcription machinery to produce changes in promoter activity (Conneely et al., 2001).

In inactive conditions, steroid hormone receptors such as estrogen are bound to chaperone proteins known as heat shock proteins (HSPs), such as hsp90, hsp70, and hsp56. In physiological conditions, steroid or estrogen hormone bonds in the receptor terminate the chaperone protein bond with the receptor, making it easier for the receptor to interact with the genome by bonding with deoxyribonucleic acid (DNA). Estrogen receptors are bound to DNA as homodimers, with dimerization occurring after release from the chaperone protein. Estrogen receptors form more stable homodimers than other steroid receptors (Beato et al., 2000; Conneely et al., 2001). The process when the chaperone protein is separated from the steroid receptor after being bound to steroid hormones causes the receptor to bind to DNA and is known as activation or transformation. This is also called steroid-dependent conformational changes from the receptor protein. However, the molecular basis of the steroid work step is unclear. After activation and dimerization, the receptor is tightly bound to a specific DNA sequence, close to the gene regulated by estrogen. The binding of receptor proteins to a specific DNA sequence is called the response element (HRE) hormone. The result is the interaction between estrogen receptors and other transcription factors and the essential transcriptional complex. This interaction affects the rate at the start of the transcription of genes, whether positive or negative.

ER mediates estrogen activity in critical physiological processes, including the development and functioning of the female reproductive system. Laudański et al. (2004) found the presence of ERα and ERβ expression in a woman's myometrium at the end of pregnancy with moderate EROP intensity and moderate/strong ERβ. Immunostaining results indicated the presence of ERα antibodies in the cell nucleus (nuclear localization), while ERβ was reported in the cytoplasm (cytoplasmic localization).

This study aimed to determine the estrogenic activity of compounds in Fatimah grass (*Anastatica hierochuntica* L.) and its potential as a phytoestrogen, with agonist targets for estrogen receptors. The samples in this study were herbal extracts of Fatimah grass (*Anastatica hierochuntica* L. family Brassicaceae) which had been dried. A phytochemical test was performed using a liquid chromatography-mass spectrometry (LCMS) method. The prediction used was based on in silico analysis using the Pass Server and Molecular Docking method by utilizing the role of computational chemistry and the online ACD/I-Lab program. Docking simulations were carried out to visualize the molecular level interactions between compounds with ERα. As a comparison, a simulation of docking between estradiol and ERα was carried out. Many studies of estrogenic activity and in silico tests in herbaceous plants have been carried out, but studies related to in silico tests on Fatimah grass compounds (*Anastatica hierochuntica* L.) have never been carried out before. Therefore, the results of this study are expected to provide information about estrogenic Fatimah grass activity and its potential as a phytoestrogen for further research related to the role of Fatimah grass (*Anastatica hierochuntica* L.) in childbirth.

MATERIALS AND METHODS

Phytochemical Analysis:

Phytochemical tests of Fatimah grass extract (*Anastatica hierochuntica* L.) using the LCMS method involves a chemical analytical technique that combines the physical separation capability of liquid chromatography (or HPLC) with the ability for mass analysis of mass spectrometry (MS). Layered chromatography or the MS system is often used in the chemical analysis because the ability of each technique is improved synergistically. Liquid chromatography separates the mixture with several components, while mass spectrometry provides the structural identity of each component with high molecular specificity and detection sensitivity. This technique can be used to analyze biochemical, organic and inorganic compounds that are commonly found in complex samples from the environment and biology. The LCMS procedure used for the phytochemical test of Fatimah grass (*Anastatica hierochuntica* L.) in this study was started by dissolving 100-250 g of smooth *Anastatica hierochuntica* L. into 95% ethanol at a ratio of 1:5 by maceration and centrifugation at 5000 rpm for 20 minutes. The supernatant obtained was further processed to purify the extract or was purified before proceeding to the LCMS test with the computer program LCMS Solution for Windows. The data were processed using the PostRun LCMS. The test results were used to determine the compounds in Fatimah grass (*Anastatica hierochuntica* L.) that will be used to assess estrogenic activity based on the in silico tests.

Target Identification:

The three-dimensional structure of estradiol, which is associated with estrogenic and estrogen receptor activity and which will be used in the docking process, was obtained from the Protein Data Bank (GDP) via http://www.rscb.org with GDP ID: 1ERE and stored in the form of PDB format (* pdb); unnecessary molecules (ligands and water) were removed using PyMol software.

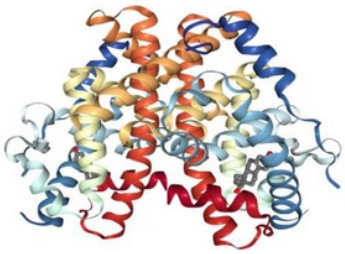


Figure 1. 3D Structure of human estrogen receptor ligand-binding domain in complex with 17beta-estradiol **(1ERE)**

Ligand Identification:

Ligand preparation was done by downloading the active compound ligands from Fatimah grass through PubChem (http://pubchem.ncbi.nlm.nih.gov), and then the 2D structures were stored in SDF format (* sdf). Each ligand structure was made in the SDF format and then converted to GDP format for doctrinal studies. The 3D structure of the ligand is shown in Figure 2.

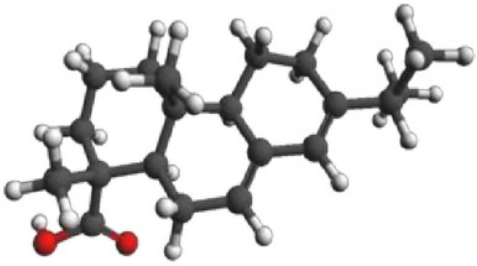
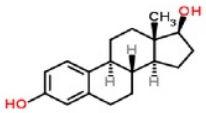
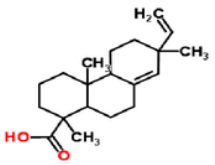
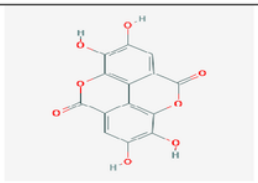
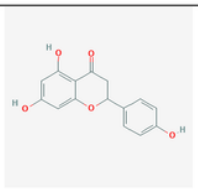
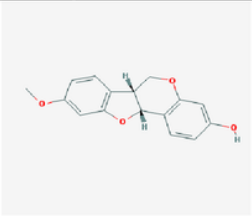


Figure 2. The 3D structure of isopimaric acid (CID: 442048)

Table 1. The Pubchem ID & Structure of reference endogenous estrogens and selected dietary compounds.

No	Compound	(Pubchem CID)	Mol Formula/ Mol wt	Structure/SMILES Notation /IUPAC Name
1	17-beta estradiol /Estradiol/ Dihydrofollic ulin	5757	$C_{18}H_{24}O_2$ 272.388 g/mol	 SMILES: CC12CCC3C(C1CCC2O)CCC4=C3C=CC(=C4)O IUPAC Name: (8R,9S,13S,14S,17S)-13 methyl6,7,8,9,11,12,14,15,16,17decahydrocyclopenta[a]phenanthrene-3,17-diol

2	Isopimaric Acid	442048	$C_{20}H_{30}O_2$ 302.458 g/mol	 SMILES: CC1(CCC2C(=C)CC3C2(CCCC3(C)C(=O)O)C)C1)C=C IUPAC Name: (1R,4aR,4bS,7S,10aR)-7-ethenyl-1,4a,7-trimethyl-3,4,4b,5,6,8,10,10a-octahydro-2H-phenanthrene-1-carboxylic acid
3	Ellagic acid	5281855	$C_{14}H_6O_8$ 302.194 g/mol	 SMILES: C1=C2C3=C(C(=C1O)O)OC(=O)C4=CC(=C(C(=C43)OC2=O)O)O IUPAC Name: InChI=1S/C14H6O8/c15-5-1-3-7-8-4(14(20)22-11(7)9(5)17)2-6(16)10(18)12(8)21-13(3)19/h1-2,15-18H
4	Naringenin	932	$C_{15}H_{12}O_5$ 272.256 g/mol	 SMILES: C1C(OC2=CC(=CC(=C2C1=O)O)O)C3=CC=C(C=C3)O IUPAC Name: 5,7-dihydroxy-2-(4-hydroxyphenyl)-2,3-dihydrochromen-4-one
5	Medicarpin	336327	$C_{16}H_{14}O_4$ 270.284 g/mol	 SMILES: COC1=CC2=C(C=C1)C3COC4=C(C3O2)C=CC(=C4)O IUPAC Name: (6aR,11aR)-9-methoxy-6a,11a-dihydro-6H-[1]benzofuro[3,2-c]chromen-3-ol

Molecular Docking:

Protein-ligand docking studies were carried out based on the crystal structure of human α-estrogen receptors. The software used for docking was Autodock Vina in PyRx v.0.8. The molecular docking method was used to predict the interactions that occur between two or more molecules and

the strength of the docking score as well as the type of bond that occurs. The principle in docking is to tether a ligand (Fatimah grass compound) to the active site of the receptor (estrogen receptor). The docking results were stored in PDB format and the binding affinity value data were stored in Microsoft Excel software. Ligands in this molecular docking process were all compounds that can be found in Fatimah grass (*Anastatica hierochuntica* L.) which were identified from the phytochemical test results using the LCMS method. The visualization of docking results only used the compounds that were chosen due to the greatest potential as phytoestrogens.

The 2D Docking Results Visualization:

The 2D bond type was analyzed using Discovery Studio v.2016 software. This visualization can be used to analyze the type of bond and the distance between the molecules that interact.

Processing and data analysis techniques:

The molecular docking analysis using the PyRx program was used to determine the interaction between the estrogen receptor and bioactive Fatimah grass. It was determined based on the affinity score binding i.e. the more negative score of affinity, that the interaction between macromolecules (receptors) and ligands (compounds) were better. The lower the docking score produced, the stronger the ligand-receptor affinity (Gilson and Zhou 2007) (while the prediction of the active compounds activity in Fatimah grass on estrogen receptor agonists using PASS SERVER gave an average activity score of at least 0.7 which means that the compound computationally has potential as a phytoestrogen).

RESULTS AND DISCUSSION

The Bioactive Compounds Found in *Anastatica hierochuntica L.*

Phytochemical analysis results showed that the ethanol extract of *Anastatica hierochuntica* L contained 75 kinds of active compounds, mainly consisting of most flavonoid, phenolic, and organic acids and a small portion of diterpene, triterpenes, sesquiterpenes and sterols. Meanwhile, only 20 of the 75 compounds found in *Anastatica hierochuntica* L. ethanol extract were estimated to have greater estrogenic activity potential than other compounds (Table 2).

Table. The 20 bioactive compounds found in Fatimah grass that were selected

No	Compound Name	Molecular Weight (g/mol)	Group	Composition (%)
1	**Isopimaric acid**	302.45	Diterpene	0.33186
2	Ellagic acid	302.19	Phenolic	3.31892
3	Naringenin	272.25	Flavanoid	2.59025
4	Medicarpin	270.28	Pterocarpane	1.12839
5	Sugetriol	252.35	Sesquiterpene	1.00152
6	Chlorogenic acid	354.31	Organic acid	1.73833
7	Anthracene	178.23	Polycyclic aromatic hydrocarbon	1.18165
8	Palustric acid	302.45	Organic acid	0.26471
9	Apigenin	270.24	Flavonoid	1.98546
10	Caryophyllene	204.35	Sesquiterpene	2.60233
11	Levopimaric acid	302.45	Diterpene	0.24025
12	Luteolin	302.45	Diterpene	0.24025

13	δ Cadinene	204.35	Sesquiterpene	0.36135
14	Chrysin	254.24	Flavonoid	1.97967
15	Genistein	270.24	Isoflavonoid	0.19306
16	Daidzein	254.24	Isoflavonoid	0.26501
17	β Selinene	204.35	Sesquiterpene	0.60812
18	Irisresorcinol	318.49	Phenolic alkene	4.80996
19	Kaempferol	286.24	Flavonol	1.91508
20	Quercetin	302.24	Flavonol	2.65521

The Activities Prediction of *Anastatica hierochuntica L*

The prediction was conducted using PASS SERVER. It was shown that active compounds in Fatimah grass have low activity against estrogen receptor agonists because the average value of activity obtained was low (<0.3). This indicates that the compound has predicted potential as a phytoestrogen based on the computational analysis (Goel, 2011) (Figure 3).

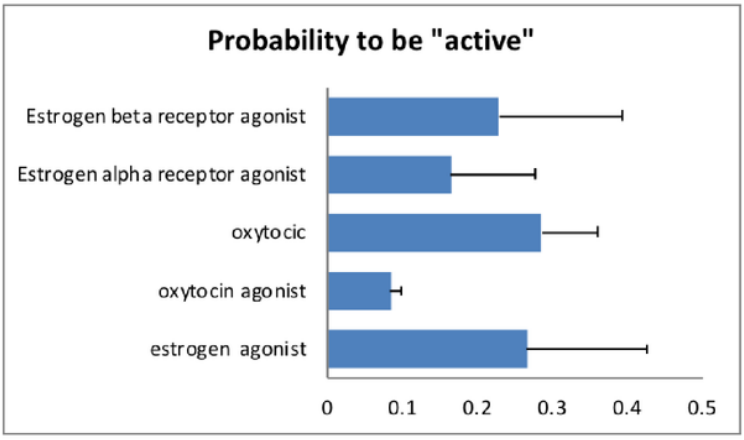


Figure 3. The active compound activity of Fatimah grass towards the estrogen receptor agonist

Molecular Docking of *Anastatica hierochuntica* L

Molecular docking was carried out using the PyRx program to determine the interaction between macromolecules (receptors) and ligands (compounds) (Figure 4).

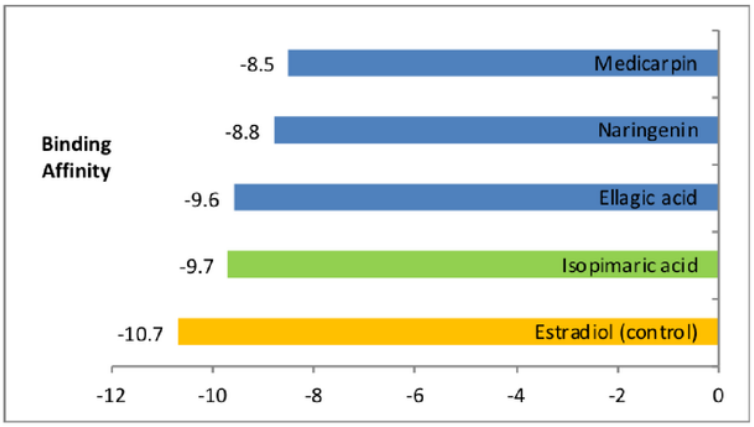


Figure 4. The score of Fatimah grass active compounds binding affinity to agonist estrogen receptor (Kcal/mol)

The binding affinity value of isopimaric acid was -9.7, ellagic acid was -9.6, naringenin was -8.8 and medicarpin was -8.5. This means that isopimaric acid and allagic acid had potential activities likes those of estradiol because the binding affinity value was close to -10.7, while Naringenin and medicarpin have lower binding affinities. This indicated that the more negative score of binding affinity resulted in a better interaction between macromolecules (receptors) and ligands (compounds) because it only needs a small amount of energy to interact. Based on these results, isopimaric acid was predicted to be a phytoestrogen, while Naringenin and Medicarpin compounds were predicted to have smaller phytoestrogen potential than Isopimaric acid and Ellagic acid.

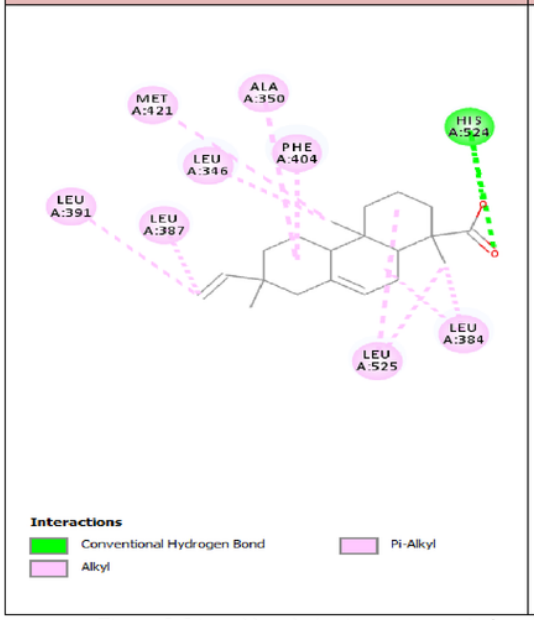
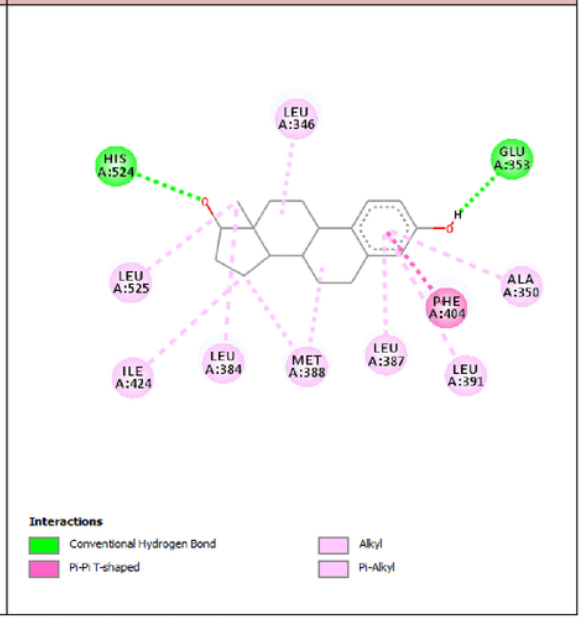
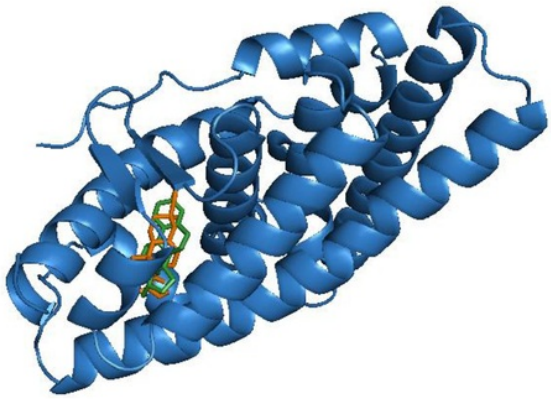
The 2D Visualization of Isopimaric acid	The 2D Visualization of Estradiol
	

Figure 5. Ligand bonds (active compounds found in Fatimah grass) on the estrogen receptor active site

It is clearly shown that ligand bonds of isopimaric acid at estrogen receptors occur at amino acids Leu391, Ala350, Leu387, Leu346, Phe404, Leu525, and Leu384, which were the same as the estradiol bonds in estrogen receptors. Other bonds of isopimaric acid with estrogen receptors occur at amino acid Met421, whereas estradiol binds to Met388 (Figure 5).



Note: Blue: estrogen receptor, orange: Isopimaric acid, green: estradiol

Figure 6. The 3D structure of isopimaric acid and estradiol

DISCUSSION

The results showed that the active compounds contained in Fatimah grass had low activity against estrogen receptor agonists for both the α-estrogen receptor and β-estrogen receptor, as well as estrogen agonists (mean value <0.3). These results were obtained from the overall analysis of active compounds in Fatimah grass using the Pass server program. This indicates that the active compounds in Fatimah grass are also predicted to have an ability as phytoestrogens based on the computational analysis, but are still not analyzed based on the *in vivo* analysis (Goel, 2011). However, from the results of the docking analysis, some active compounds in Fatimah grass (*Anastatica hierochuntica* L.) have potential as phytoestrogens based on docking scores. It is assumed that isopimaric acid, ellagic acid, naringenin and medicarpin compounds have potential as phytoestrogens because they have a large binding affinity score close to that of estradiol as a control. This binding ability of phytoestrogens can help to predict their activity in selective tissue based on the expression of estrogen receptor subtypes in specific tissues. A similar competitive molecular docking approach has also been used for agonists and antagonists of estrogen alpha (ERα) receptors (Ng H. W., 2014). ERα has three specific binding sites i.e. ligand binding domain (AF-2), against growth factor (AF-1) and the DNA domain (DNA-binding domain). Ligands that bind to estrogen receptors and compete with estrogen are called selective estrogen receptor modulators (SERMs). SERM compounds can act as antagonists or agonists depending on the location of the receptors on the target tissue; this is due to different tissues having different ERα conformations (Putra, 2008).

Phytoestrogens are a substrate of plants that have estrogen-like properties; although its chemical properties are different from those of estrogen, it has a nucleus that is exactly the same. Estrogenic properties occur because phytoestrogens also have 2-OH/hydroxyl groups that are 11.0-11.5 A0 in essence, which is exactly the same as the estrogen nucleus itself. The researchers agree the

distance of 11 A0 and this -OH group is the main structure of a substrate to have an estrogenic effect, which has a certain affinity that able to occupy estrogen receptors (Achadiat 2007). Phytoestrogens will have estrogenic effects if they bind to estrogen receptors, but the affinity of phytoestrogens against estrogen receptors is lower than that of endogenous estrogen. Bonds of phytoestrogens or herbal estrogens with estrogen receptors produce a pro-estrogenic or anti-estrogenic effect on the target tissue. The response depends on the amount of estrogen and estrogen receptor produced. Phytoestrogens are compounds that are naturally formed and are found in plants. Phytoestrogens are contained in plant tissues in the form of glycosides, which are soluble in water. Phytoestrogens are identified as plant substances that are structurally and functionally similar to estradiol (Knight, Wall & Eden 1999). Several studies have succeeded in obtaining an overview of the effects of phytoestrogens, including their ability to bind to estrogen receptors on target organs and induce gene products that have a specific response to estrogen (Kurzer 1997). Phytoestrogens have estrogenic properties and receptors similar to 17β-estradiol (Lissin et al., 2000).

The prediction of the phytoestrogen effects based on the *in vivo* analysis is more difficult due to the route of administration, the chemical form of the phytoestrogens, metabolism, bioavailability, half-life, time and level of exposure, intrinsic estrogenic state and non-hormonal secondary mediation of phytoestrogens. The potential of Fatimah grass extract (*Anastatica hierochuntica* L.) as a phytoestrogen through *in vivo* research showed that the administration of Fatimah grass extract with a dose of 100 mg/KgBW for 5 days could increase estrogen alpha (ERα) receptor expression compared to controls (Astutik, 2011). However, from these results, the active compounds that act as ligands in binding to estrogen receptors are unknown. Based on the results of docking tests on active compounds in the extract of Fatimah grass, it can be seen that some compounds in Fatimah grass can bind to estrogen receptors and have a great affinity, including Isopimaric acid, Ellagic acid, Naringenin and Medicarpin. By binding to the ligand on the receptor, there is stimulation of the protein receptor, resulting in a change in shape, which results in the receptor-ligand complex becoming active. This complex enters the cell nucleus and is thought to be bound by certain components of chromatin or genetic material. This causes the activity of genes to change and stimulates the formation of DNA (Deoxyribonucleic Acid) through RNA (Ribonucleic Acid).

Isopimaric acid is a member of the resinous acids group in the form of tricyclic diterpene, which has a thick three-ring structure, one carboxyl group and a double bond (conjugated). Isopimaric acid and several other compounds in Fatimah grass (*Anastatica hierochuntica* L.) can bind to human estrogen receptors with different affinity. This can be seen from the docking score of compounds in the Fatimah grass with estrogen receptors. The results showed that isopimaric acid had the highest docking score compared to other active compounds in Fatimah grass (*Anastatica hierochuntica* L.) including flavonoid compounds that are widely found in Fatimah grass, which is close to endogenous estrogen docking score, estradiol. This shows a significant similarity between the *in vivo* test and the in silico approach to estrogen definitively from plant-derived compounds. Therefore, the in silico study is very important in screening & predicting the activities of a large number of compounds including estrogenic activity. Conceptually, isopimaric acid is a compound that acts as a major distributor of calcium (Ca^{2+}) in cells by activating the opening of potassium (K^{+}) channels after binding to receptors. Therefore, through this in silico test, it is also possible to analyze the role of Fatimah grass extract herbs in activating transduction signals in cells and gene transcription processes using pathway analysis. Thus, these findings indicate that the active compounds in Fatimah grass have estrogenic effects and are predicted to be phytoestrogens that may play a role in the reproductive process.

CONCLUSION

In conclusion, isopimaric acid is one of the estrogen receptor ligands found in Fatimah grass (*Anastatica hierochuntica* L.) which provided the greatest affinity and good potential as phytoestrogens. Therefore, the results presented here are important for the faster and cheaper screening of a large number of plant-derived compounds such as for estrogenicity to discover drugs.

ACKNOWLEDGEMENT

This research was financially supported by Pusat Peningkatan Mutu dan Sertifikasi Pendidik for Lecture's Scholar related to Kementerian Kesehatan RI. Thanks to Shimadzu Laboratory that facilitated this research with LCMS and InBio Indonesia of Universitas Brawijaya Malang that help to perform the in silico test.

(1) Similar studies must be carried out to predict the activity of compounds in signaling activity for gene transduction and transcription.
(2) The results of this study can be used as a basis for further research in predicting the uterotonic activity of Fatimah grass extract in silico.
(3) The results of this study can be used as a reference in pharmacological studies of compound activity in designing drugs.

REFERENCES

Achadiat C.M., 2007. Fitoestrogen untuk Wanita Menopause, artikel, tersedia di http://www.mitrainti.org/?q=node/32, diakses pada tgl. November 2016

Astutik, H., 2011. EkstrakRumput Fatimah Dan EkspresiReseptor Estrogen (ER α) Sel Miometrium. *Jurnal Kesehatan*, Poltekkes Malang, Edisi Mei, Vol 9, No1, hal 22-34.

Beato, M & Klug, J 2000, 'Steroid hormone receptors: an update', *Human Reprod* update, vol. 6, no. 3, pp. 225-236.

Breinholt, V, Hossaini, A, Svendsen, GW, Brouwer, C & Nielsen, SE., 2000. 'Estrogenic activity of flavonoids in mice. The importance of estrogen receptor distribution, metabolism and bioavailability', doi:10.1016/S02786915_(00)00046-6 , Available online 25 August 2000, http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6T6P-4123CNB.

Brzozowski, A.M., Pike, A.C., Dauter, Z., Hubbard, R.E., Bonn, T., Engstrom, O., Ohman, L., Greene, G.L., Gustafsson, J.A., Carlquist, M., 1997, Molecular basis of agonism and antagonism in the oestrogen receptor, Nature 389**: 753-758,** PubMed**: 9338790,** DOI**:** 10.1038/39645

Conneely, M., 2001. 'Perspective: female steroid hormone action', *Endocrinology*, vol. 142, no. 6, pp.2194-2199.

Gilson MK, Zhou HX. 2007. Calculation of protein-ligand binding affinities. Annu Rev Biophys Biomol Struct. ;36:21–42. doi: 10.1146/annurev.biophys.36.040306.132550.

Goel R.K., Singh D., Lagunin A., Poroikov V. (2011). PASS-assisted exploration of new therapeutic potential of natural products. *Med. Chem. Res.*, 20 (9), 1509-1514.

Knight DC, Wall, PL, and Eden JA., (1999). A Review of Phytoestrogen and their relation to menopausal symptoms, Center for Management of The Menopausal, Royal Hospital for Woman Sydney.

Kuiper G. G., Lemmen J. G., Carlsson B. et al. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. Endocrinology. 1998; 139(10), 4253-63. 6. Morito K., Hirose T., Kinjo J., Hirakawa T., Okawa M., Nohara T. Interaction of phytoestrogens with estrogen receptors α and β. Biol. Pharm. Bull. 2001; 25(1), 48-52

Kuiper, GG, Carlsson B, Grandien, K, Enmark, E, Haggblad, J, Nilsson, S &Gustafsson, JA., 1997. 'Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta', *Endocrinology*, no. 138, pp. 863–870.

Kurzer, SM. and Xia Xu, 1997. Dietary Phytoesytrogens : Annual Review of Nutrition, vol. 17 : 353-381. https://doi.org/10/1146/annurev.nutr.17.1.353

Laudański, P, Redźko, S, Przepieść, J, Koda, M, Wołczyński, S, Sulkowski, S & Urban, J., 2004. 'Expression of estrogen receptors α and β in term human myometrium', *Biology of reproduction,* Vol. 4, No. 3 305, Medical University of Białystok, Białystok, Poland, pp.305-310.

Lissin, LW & Cooke, JP 2000, 'Phytoestrogens and Cardiovascular Health', *Journal Am Coll Cardiol,* no 35, pp.1403 – 1410.

Mohamed, AA, Khalil, AA, & El-beltagi, HES, 2009. 'Chemical compositions and antioxidant/antimicrobial activities of kaff maryam (anastatica hierochuntica) and doum palm (hyphaenethebaica) cultivated in Egypt', *BiyolojiBilimleriAraştırma Dergisi* 2 (*BIBAD).* ISSN:1308-3961, no.2, pp. 71-79.

Nitu Debnath, Monjur Ahmed Laskar and Anupam Das Talukdar, 2016. Studies on in silico estrogenicity and prediction of drug ability of Genistein and Coumestrol with respect to human estrogen receptors, International Research Journal of Pharmaceutical and Biosciences, ISSN: 2394 - 5826 http://www.irjpbs.com, e-ISSN: 2394 - 5834

Ng H. W., Zhang W., Shu M., Luo H., Ge W., Perkins R., Tong W., Hong H., 2014. Competitive molecular docking approach for predicting estrogen receptor subtype a agonists and antagonists. BMC Bioinformatics; 15(Suppl. 11):S4

Norden, H &Havnen, C., 2005, 'Impact of socio-demographic factors, knowledge and attitude on the use of herbal drugs in pregnancy', *ActaObstetGynecoScandl*.no. 84, pp. 26-33.

Pike A. C., Brzozowski A. M., Hubbard R. E., Bonn T., Thorsell A. G. and Engstrom O. Structure of the ligand-binding domain of oestrogen receptor beta in the presence of a partial agonist and a full antagonist. The EMBO journal. 1999; 18: 4608-18.

Putra, I.G.N.S., Nurcahya,B.M., Rachmattika, B., Wynanda, Sudarmanto, B.S. A., Meiyanto, E., 2008. Kurkumin dan Analognya sebagai *Selective Estrogen Receptor* Modulators (SERMS) : Kajian Berdasarkan Metode Docking pada Reseptor Estrogen Alfa, Pharmacon, 9 (1), 7-9.

Rizk, AM, Hammouda, FM, Ismail, SI, Hassan, NM & Ahmed, FA., 1993. 'Constituents of Plants Growing in Qatar XX. Phytochemical Investigation of *Anastatica Hierochuntica*', *Pharmaceutical Biology*, Volume 31, Issue 4 October 1993 pages 327 – 329, diaksestanggal 17 Desember 2009. http://www.informaworld.com/smpp/content~content=a786713708&db

Siti Rosmani Md Zin, Mohammad A. Alshawsh, Normadiah M. KassimU, Noor Eliza Hashim, Zahurin Mohamed, 2017. Biological activities of *Anastatica hierochuntica* L.: A systematic review, Biomedicine & Pharmacotherapy [IF: 2.76], DOI | 10.1016/j.biopha.2017.05.011

cj976

ORIGINALITY REPORT

17%	%	17%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	A. M. Rizk. "Constituents of Plants Growing in Qatar XX. Phytochemical Investigation of Anastatica Hierochuntica: NOTE", Pharmaceutical Biology, 10/1/1993 Publication	1%
2	Nahoum, V.. "Androgen and estrogen receptors: Potential of crystallography in the fight against cancer", International Journal of Biochemistry and Cell Biology, 200707 Publication	1%
3	Raya Salim Al-Farsi, Mushtaque Ahmed, Ahmed Al-Busaidi, B.S. Choudri. "Translocation of pharmaceuticals and personal care products (PPCPs) into plant tissues: A review", Emerging Contaminants, 2018 Publication	1%
4	Peter Collins. "Raloxifene acutely suppresses ventricular myocyte contractility through inhibition of the L-type calcium current", British Journal of Pharmacology, 05/2004 Publication	1%

5	Hui Wen Ng, Stephen W. Doughty, Heng Luo, Hao Ye, Weigong Ge, Weida Tong, Huixiao Hong. "Development and Validation of Decision Forest Model for Estrogen Receptor Binding Prediction of Chemicals Using Large Data Sets", Chemical Research in Toxicology, 2015 Publication	1%
6	Kenneth Dr Setchell. "Soy and other legumes: 'Bean' around a long time but are they the 'superfoods' of the millennium and what are the safety issues for their constituent phytoestrogens?", Asia Pacific Journal of Clinical Nutrition, 10/2000 Publication	1%
7	Merilin Al Sharif, Petko Alov, Vessela Vitcheva, Antonia Diukendjieva, Mattia Mori, Bruno Botta, Ivanka Tsakovska, Ilza Pajeva. "Natural modulators of nonalcoholic fatty liver disease: Mode of action analysis and in silico ADME-Tox prediction", Toxicology and Applied Pharmacology, 2017 Publication	1%
8	Siti Rosmani Md Zin, Normadiah M. Kassim, Mohammed A. Alshawsh, Noor Eliza Hashim, Zahurin Mohamed. "Biological activities of Anastatica hierochuntica L.: A systematic review", Biomedicine & Pharmacotherapy, 2017 Publication	1%

9	Mijo Simunovic. "Mechanism and thermodynamics of ligand binding to auxin amidohydrolase", Journal of Molecular Recognition, 09/2011 Publication	1%
10	Wang, Si, Jac M. M. J. G. Aarts, Laura H. J. de Haan, Dimitrios Argyriou, Ad A. C. M. Peijnenburg, Ivonne M. C. M. Rietjens, and Toine F. H. Bovee. "Towards an integrated in vitro strategy for estrogenicity testing : Towards an integrated in vitro strategy for estrogenicity testing", Journal of Applied Toxicology, 2013. Publication	1%
11	Stefan Brandmaier, Igor V Tetko. "ROBUSTNESS IN EXPERIMENTAL DESIGN: A STUDY ON THE RELIABILITY OF SELECTION APPROACHES", Computational and Structural Biotechnology Journal, 2013 Publication	1%
12	Evelyn Wolfram, Adriana Trifan. "Computational Aids for Assessing Bioactivities", Elsevier BV, 2018 Publication	1%
13	Kenneth D. R. Setchell, Aedin Cassidy. "Dietary Isoflavones: Biological Effects and Relevance to Human Health", The Journal of Nutrition,	1%

1999
Publication

14	Graziano Ceresini. "Estrogen Receptor (ER)-?, But Not ER-?, Is Present in Thyroid Vessels: Immunohistochemical Evaluations in Multinodular Goiter and Papillary Thyroid Carcinoma", Thyroid, 12/2006 Publication	1%
15	"Antibacterial and antifungal screening of four medicinal plants", Journal of Coastal Life Medicine, 2014 Publication	<1%
16	Anklesaria, Behram. "The promise of phytoestrogens.", Indian Journal of Pharmacology, July-August 2011 Issue Publication	<1%
17	T Mikkola. "Estrogen replacement therapy, atherosclerosis, and vascular function", Cardiovascular Research, 02/15/2002 Publication	<1%
18	Lisa McKenna. "What over-the-counter preparations are pregnant women taking? A literature review", Journal of Advanced Nursing, 12/2006 Publication	<1%
19	Elena Chaves-Pozo, Isabel Cabas, Alfonsa Garca-Ayal. "Chapter 2 Sex Steroids Modulate	<1%

Fish Immune Response", InTech, 2012
Publication

---

20 Abla Alzagameem, Basma El Khaldi-Hansen, Birgit Kamm, Margit Schulze. "Chapter 5 Lignocellulosic Biomass for Energy, Biofuels, Biomaterials, and Chemicals", Springer Nature, 2018
Publication

<1%

---

21 Powers, Chelsea N, and William N Setzer. "A molecular docking study of phytochemical estrogen mimics from dietary herbal supplements", In Silico Pharmacology, 2015.
Publication

<1%

---

22 Victoria Raks, Hossam Al-Suod, Bogusław Buszewski. "Isolation, Separation, and Preconcentration of Biologically Active Compounds from Plant Matrices by Extraction Techniques", Chromatographia, 2017
Publication

<1%

---

23 "20th International Congress of Nutrition: Granada, Spain, September 15 20, 2013", Annals of Nutrition and Metabolism, 2013
Publication

<1%

---

24 -, Haryono, Soemarno -, Surjono -, Imam Hanafi, and Anwar Fitrianto. "Modeling Spatial Development Relationship between Sub districts: Case study in Ngawi, East Java,

<1%

Indonesia", Review of European Studies, 2015.
Publication

---

25 Christian J. Gruber. "Production and Actions of Estrogens", New England Journal of Medicine, 01/31/2002 <1%
Publication

---

26 Svetlana Trifunović, Verica Milošević. "The Morpho-Functional Parameters of Rat Pituitary Hormone Producing Cells After Genistein Treatment", Macedonian Veterinary Review, 2018 <1%
Publication

---

27 Delgado, Amélia Martins, Maria Daniel Vaz Almeida, and Salvatore Parisi. "Greens and Other Vegetable Foods", Chemistry of the Mediterranean Diet, 2017. <1%
Publication

---

28 Guadarrama, P.. "Construction of simplified models to simulate estrogenic disruptions by esters of 4-hydroxy benzoic acid (parabens)", Biophysical Chemistry, 200809 <1%
Publication

---

29 Branislav Radović. "Genistein and other soya isoflavones are potent ligands for transthyretin in serum and cerebrospinal fluid", British Journal Of Nutrition, 06/2006 <1%
Publication

30	Edi Murwani, Stefanus Supriyanto, Suharto Suharto. "Organizational Commitment Can Improve Compliance of Blood Transfusion Procedure", International Journal of Public Health Science (IJPHS), 2016 Publication	<1%
31	Casini, Maria Luisa, Sandro Gerli, and Vittorio Unfer. "An infertile couple suffering from oligospermia by partial sperm maturation arrest: Can phytoestrogens play a therapeutic role? A case report study", Gynecological Endocrinology, 2006. Publication	<1%
32	Duffy, M. J.. "Estrogen Receptors: Role in Breast Cancer", Critical Reviews in Clinical Laboratory Sciences, 2006. Publication	<1%
33	ULRICH MEVE. "A morphological, karyological and chemical study of the Apteranthes (Caralluma) europaea complex", Botanical Journal of the Linnean Society, 12/2005 Publication	<1%
34	N KASE. "The Normal Human Ovary Part IIHow Steroid Hormones Work", Diagnosis and Management of Ovarian Disorders, 2004 Publication	<1%
	Wolohan, P.. "Use of binding energy in	

35	comparative molecular field analysis of isoform selective estrogen receptor ligands", Journal of Molecular Graphics and Modelling, 200409 Publication	<1%
36	Emanuele Amata, Agostino Marrazzo, Maria Dichiara, Maria N. Modica et al. "Comprehensive data on a 2D-QSAR model for Heme Oxygenase isoform 1 inhibitors", Data in Brief, 2017 Publication	<1%
37	N. X. Tan. "Prediction of chemical carcinogenicity by machine learning approaches", SAR and QSAR in Environmental Research, 01/2009 Publication	<1%
38	Gaponov, Alexandr A., Elena T. Zlenko, Svetlana V. Shishkina, Oleg V. Shishkin, Oleksii M. Antypenko, Serhii V. Tretiakov, and Vitaliy A. Palchikov. "Synthesis, spectroscopic characterization, X-ray structure, and in vivo neurotropic activity of new 1,5-benzodiazepin-2-ones", Medicinal Chemistry Research, 2016. Publication	<1%
39	Ascenzi, P.. "Structure-function relationship of estrogen receptor @a and @b: Impact on human health", Molecular Aspects of Medicine, 200608 Publication	<1%

40	Mense, Sarah M. Hei, Tom K. Ganju, Rames. "Phytoestrogens and breast cancer prevention: possible mechanisms of action.(Review)", Environmental Health Perspectives, April 2008 Issue Publication	<1%
41	"Poster presentation abstracts", Medicinal Chemistry Research, 02/2010 Publication	<1%
42	Opalka, Dr. M., B. Kaminska, M.K. Piskula, H. Puchajda-Skowronska, and L. Dusza. "Effects of phytoestrogens on testosterone secretion by Leydig cells from Biłgoraj ganders (Anser anser)", British Poultry Science, 2006. Publication	<1%

Exclude quotes	Off	Exclude matches	Off
Exclude bibliography	Off		