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IN SILICO STUDY OF INHIBITION OF ACTIVATION OF 1A52 ETHANOL EXTRACT LEUNCA FRUIT (*Solanum nigrum* L)

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ABSTRACT

The development of science has found a way to prevent skin aging in menopausal women. One of the therapies is estrogen replacement therapy (17β estradiol). Skin aging in menopausal women is associated with decreased ERα expression. Leunca fruit (Solanum nigrum L) is known to contain phytoestrogens and has the potential as an antiaging agent. The purpose of this study was to predict the anti-aging effect of Solanum nigrum ethanol extract compounds through the Erα 1A52 [A] activation pathway. The research method of active substance analysis metabolite profiling was carried out by analyzing physicochemical properties using pkCSM. This analysis was carried out as an initial selection of compound safety for therapy. Molecular docking with the MVD (Free trial) application. The RMSD value ≤ 2Å indicates a valid docking and the application can be used. The results of the in silico study showed that the results of metabolite profiling showed that diosgenin was an agonist against ERα. The compound has physicochemical properties according to the Lipinski standard so that it can bind to ERα. The conclusion is that diosgenin has the potential and can act as a 1A52 [A] inhibitor so it can be used as an antiaging agent.

Keywords **:** *Solanum nigrum, Diosgenin, Aging.*

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INTRODUCTION

As you get older , your skin will experience an aging process. Aging can be caused by intrinsic and extrinsic factors. The intrinsic factors that play a role are genetics, cell metabolism, and hormones. Apart from that, there are extrinsic factors such as ultraviolet radiation, infrared, free radicals, environmental carcinogens which also play a role in skin aging (1). Free radicals under normal circumstances The amount is beneficial for health such as helping host cells protect our body from pathogens cells and to regulate intracellular flow in some cell types. Meanwhile, in excessive amounts this can cause oxidative stress (2). These two factors cause changes in all layers of the skin, both from inside and outside the body. One of the factors that causes premature aging is estrogen deficiency.

Estrogen deficiency is one of the hormonal factors that can cause premature aging (3) . Estrogen deficiency is a condition where there is a decrease in the activity of the estrogen hormone which has binding capacity with estrogen receptors (4) . During a state of estrogen deficiency, there is a decrease in the production of the estrogen hormone, which has a bad effect on the woman's body, because the estrogen hormone plays a role in cell formation and protects cells from damage. One part of the body that is affected by estrogen deficiency is the skin, so the skin experiences aging (5).

Skin aging is associated with the quality of collagen in the skin decreasing due to a reduction in the number of active estrogen receptors so that the skin experiences decreased elasticity, increased wrinkles, increased dryness and the skin becomes thinner (6). Skin aging affects women's social life, which is supported by the fact that skin is the part of the body that is most often exposed to external factors and is also the first thing an individual sees when interacting with other people, so skin aging, especially in women, will reduce self-confidence. and affect the quality of life (7). To overcome skin aging, you can use hormone replacement *therapy* (HRT) .

Phytoestrogens are a class of compounds derived from plants that have similar functions, structures or can bind to estrogen receptors and are expected to have similar effects. Phytoestrogen compounds are also reported to have activity in reducing disease complaints that arise due to estrogen deficiency (8). Phytoestrogens are classified into three categories isoflavones, coumestan, and lignans (9) . Phytoestrogens in the form of isoflavones are genistein, daidzein, glycitein, formononetin, and biochanin A (10) . Veerapagu observed that the fruit extract showed significant antioxidant activity with an

IC50 value of 70.73 μg/ml for scavenging DPPH radicals and an IC50 of 59.72 μg/ml for scavenging Hydrogen peroxide. (11) . Flavonoid molecules are the most abundant compounds that function as natural antioxidants . As antioxidants, flavonoids can provide radical molecules with hydrogen atoms (12) .

Recent studies prove that isoflavones are *selective estrogen receptor modulator* (SERM) because it can act as estrogen in certain tissues such as bones and act as anti-estrogen in other tissues, namely the breast and uterus (13) . One source of isoflavones is leunca fruit. Leunca is a type of eggplant plant. The results of phytochemical screening showed the presence of alkaloids, flavonoids, tannins, saponins, and steroids/triterpenoids. Based on the results of previous research, it was reported that leunca contains isoflavones with the highest levels of glycitein, followed by genistin, daidzein, and genistein each at 375.0844; 109.2039; 15.6771, and 1.0029 mg/100 g (14) . Testing the estrogenic potential of the methanol extract of the glycoside fraction of leunca fruit at a concentration of 40 μg/ml can induce an increase in MCF-7 cell proliferation while an extract concentration of 80-320 μg/ml causes progressive inhibition of cell growth (15) . Other research shows that leunca fruit extract (*Solanum nigrum*) can be used as an anti-inflammatory by inhibiting the thickening of the epidermis and dermis in the AD model induced by 1-chloro-2,4 dinittrobenzene (DNCB) which uses test animals where the control group is thicker compared to the normal group and the leunca fruit extract test animal group is thinner than the Control (16).

This research is an in silico (computational) activity test to predict effect *antiaging* on *estrogen* receptor alpha (ER-α) . *In silico* studies are computational simulation methods using certain applications and web tools to predict the activity of compounds in effort invention drug new. This approach offers the advantage of being a rapid approach to predict potential interactions between a ligand and a targeted receptor [22] before further bioactivity testing is carried out in laboratory.

MATERIAL & METHODS

Tools and materials

The Phytochemistry and Pharmacology database (17) and stored in the Structure Data File (SDF). Energy minimization of the 3D structure was performed using Datawarrior [18] and the files were saved in SDF format . The crystal structure of the Estrogen Receptor complex was

downloaded from the RSCB PDB database (www.pdb.org) and saved as a protein data bank (PDB) file. The in silico test was carried out using MVD (free trial). The computer used has Windows 11 Pro specifications, AMD Ryzen 5 CPU @ 1.90 GHz -2.11 GHz, and 16.0 GB RAM.

Preparation of proteins and ligands

Crystal structures that have been retrieved from the RSCB PDB database are imported into Molegro Virtual Docker (MVD). For molecular docking purposes, all water molecules were removed and corrections were made to the inappropriate amino acid residues. Ligand preparation was carried out using Datawarrior to find the most stable conformation or had the lowest energy (Merck Molecular Force Field value, MMFF94).

Analysis of ligand-protein interactions with molecular docking

Analysis of interactions between proteins and ligands through molecular binding was carried out using MVD on all 3D structures of ligands or *Solanum nigrum metabolite compounds* with positive druglikeness values. Previously, a re-docking process was carried out on molecules in the protein binding site region to validate the docking method used. The validity requirements for this method are determined by a Root Mean Square Deviation (RMSD) value < 2 Å. Afterwards, molecular docking is applied to the 3D structure of the ligand against the protein crystal structure . In this docking process, the parameters measured include the energy values involved, such as MolDock Score, Rerank Score, and Hbond . To evaluate the binding strength between ligands and receptor proteins, Rerank Score is often a commonly used parameter [21].

In silico ADMET analysis using pkCSM

ADMET analysis was carried out on A. muricata metabolite compounds predicted as candidate TP53RK inhibitors. The TP53RK inhibitor candidate is a metabolite compound of A. muricata with a Rerank Score value that is more negative than the Rerank Score value of ANP_301 (AMPPNP).

RESULTS AND DISCUSSION

As a result of previous research "Phytochemistry and Pharmacology" it was discovered that Solanum nigrum contains many secondary metabolites, including diosgenin which is included in the steroid group and solasonine which is included in the alkaloid group. Diosgenin and Solasonine had their 3D structures downloaded and their energy minimized using MMFF94 calculations. Native ligand (EST_1) in the crystal structure 1A52 [A] , the 3D conformation of

27 *Solanum nigrum* metabolite compounds whose energy has been minimized was imported into MVD for molecular docking analysis of the D chain of the estrogen receptor protein 1A52 [A]. The 3D structure of 1A52[A] and the EST_1 ligand contained in the 1A52[A] crystal structure can be seen in Figure 1 .

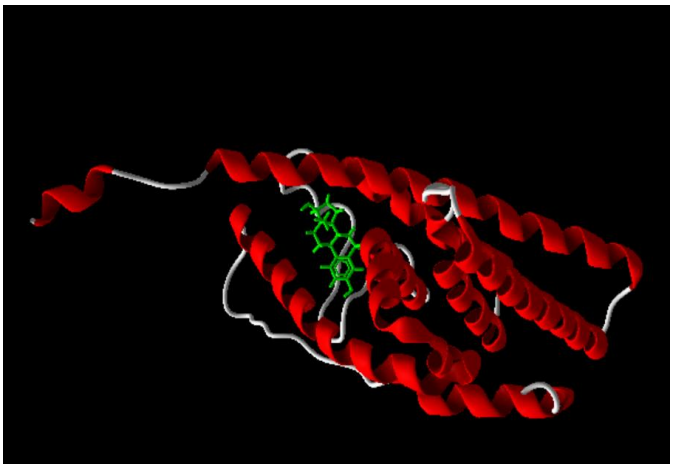


Figure 1 . Interaction between 1A52[A] protein and its crystalline ligand

Validation of the interaction of 1A52 [A] with the ligand in the crystal structure EST_ 1 through the redocking process can be seen in Figure 2. In Figure 2 it can be seen that many hydrogen bonding and steric interactions occur at the same amino acid residue . Meanwhile, the RMSD value resulting from the redocking process shows a value below 2 Å. Thus it can be concluded that the molecular docking method used is valid. After the molecular docking method was deemed valid, the next process was to carry out molecular docking between the metabolite compounds diosgenin and solasonine with 1A52[A] . The results of molecular docking can be seen in Table 1 and Figure 2 .

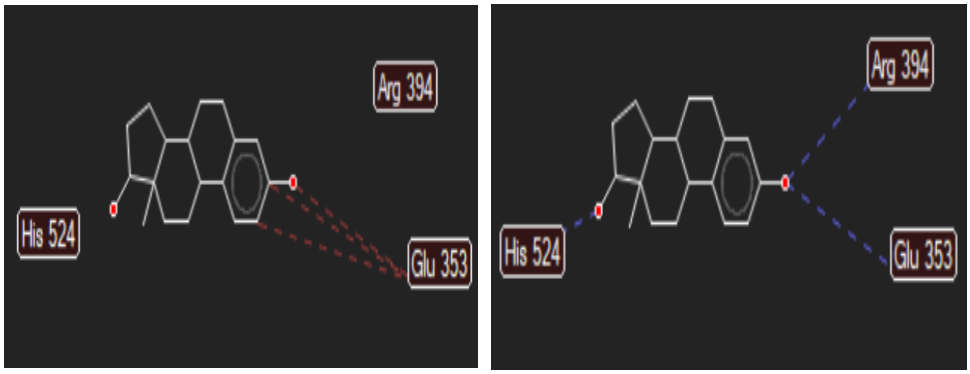


Figure 2 . Interaction of 1A52[A] with native ligand EST_1 in its crystal structure and redocking results

Information :
----- Hydrogen Bonds;
----- Steric

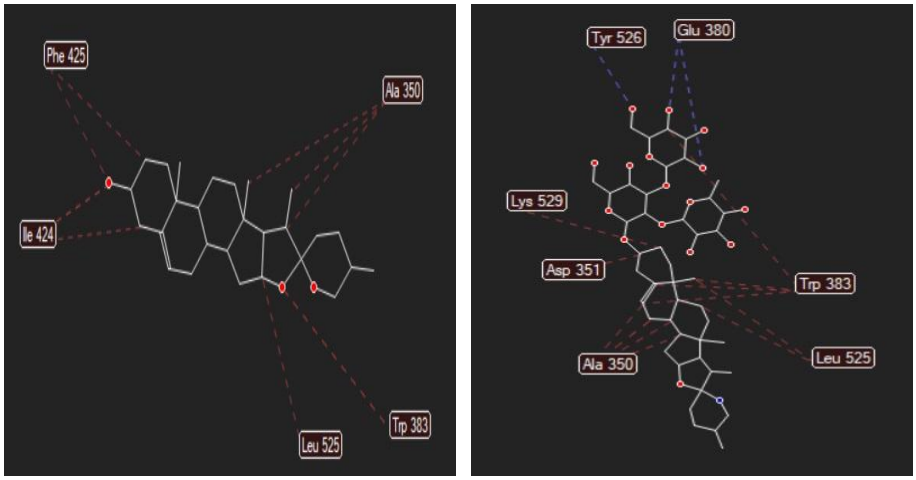
Table 1 . The value of the energy released (in the docking score) due to the interaction of TP53RK (6WQX [D]) with the native ligand (AMPPNP/ ANP_301) and the RMSD value of the redocking result

Name	*MolDock Score*	*Rerank Score*	RMSD	*Hbond*
[00] EST_1 [A]	-107,195	-92 , 5398	0 , 535661	-5 , 89692
[01] EST_1 [A]	-100,922	-87 , 8097	2 , 66342	-3 , 83894
[02] EST_1 [A]	-98,197	-52 , 9301	6 , 76675	-8 , 19813
[03] EST_1 [A]	-89.217	-74 , 3813	6 , 32961	-5 , 57661

Based on the results of molecular docking of Solanum nigrum against 1A52[A] listed in Table 1 , diosgenin Rerank Score negative is the same as EST_1[A] . Meanwhile , solasonine has a positive Rerank Score. Thus, diosgenin has potential and can act as an inhibitor of 1A52[A] . To evaluate ADMET diosgenin, it was carried out in silico using pkCSM, the results of which can be seen in Table 2 and Figure 3 .

Table 2 . Results of molecular docking of diosgenin and solasonine on 1A52[A]

Name	*MolDock Score*	*Rerank Score*	*Hbond*
[11] Diosgenin	-89.9999	-26.4688	0.0000
[00] EST_1 [A]	-106.5650	-92.4545	-5.9910
[07] Solasonine	-29.4073	18.4938	-4.0406



(a) Diosgenin (b) Solasonine

Figure 2 . Interaction of 1A52[A] with native ligands (a) diosgenin and b) solasonine

Information:
----- Hydrogen Bonds
-----Electrostatic Interactions

Rerank Score is a measure of binding affinity that combines the energy released from the interaction between the ligand and the protein, as well as the internal energy of the ligand (18). By taking into account the internal energies of ligands, such as bond torque, sp2-sp2 bonds, hydrogen bonds, Van der Waals interactions, and electrostatic interactions, Rerank Score aims to increase precision in selecting the order of ligand positions. The more negative the Rerank Score value, the more stable the bond between the ligand and receptor. A decrease in Rerank Score can also be related to an increase in compound or ligand activity. The activity coefficient can be directly connected to the Gibbs free energy or the energy released due to ligand-receptor interactions (19).

The research results of Lubomir Petrov et al stated that diosgenin is known to increase regenerative effects and provide rapid wound reduction . D iosgenin maintained high levels of non-enzymatic glutathione in wound tissue compared to other substances tested (18) . Based on this, diosgenin can be used for cell proliferation. To see the toxicity of diosgenin, see table 3.

Table 3 . Results of diosgenin analysis using pkCSM

ADMET	**Predicted Value Diosgenin**	**Criteria**
Absorption		
Water solubility	-5,911	log mol/L << (less solubility)
Caco2 permeability	1,303	Papp > 8x10 $^{-6}$ cm/s (height)
Absorption by the intestine	96,365	% Absorbed > 30% (high)
Skin Permeability	-3,185	log Kp < -2.5 (high)
P-glycoprotein substrate	No	no (high bioavailability)
P-glycoprotein I inhibitor	Yes	no (low bioavailability)
P-glycoprotein II inhibitor	Yes	no (low bioavailability)
Distribution		
VDss (human)	0.461	log L/kg > -0.15 (high)
Fraction unbound	0	the bigger, the better
BBB Permeability	0	log BB<-1 (low)
CNS permeability	-2439	log PS <-3.0 (low)
Metabolism		
CYP2D6 substrate	No	not metabolized by cytochrome P450
CYP3A4 substrate	Yes	metabolized by cytochrome P450
CYP1A2 inhibitor	No	does not affect cytochrome P450
CYP2C19 inhibitor	No	does not affect cytochrome P450
CYP2C9 inhibitor	No	does not affect cytochrome P450
CYP2D6 inhibitor	No	does not affect cytochrome P450
CYP3A4 inhibitor	No	does not affect cytochrome P450

Excretion		
Total Clearance	-44.31	log ml/min/kg
Renal OCT2 substrate	yes	yes (excreted in the kidneys)
Toxicity		
AMES Toxicity	No	(not mutagenic)
Max. initial dose	-0.165	log mg/kg/day <0.477 (low)
hERG I inhibitors	No	no (does not cause ventricular arrhythmias)
hERG II inhibitor	Yes	yes (causes ventricular arrhythmia)
Rat Acute Toxicity (LD50)	2,482	LD50 (mol/kg) > 5000 mg/kg (non-toxic) *
Chronic Oral Toxicity Rat (LOAEL)	1,341	LOAEL (mol/kg/day) > 1000 mg/kg/day (non-toxic) *
Hepatotoxicity	No	no (not toxic)
Skin Sensitization	No	no (does not cause sensitization)
T. Pyriformis toxicity	0.358	log µg/L > -0.5 (toxic)

CONCLUSION

The diosgenin content in leunca fruit (*Solanum nigrum* L) is similar to *the native ligand* (EST_1) in the 1A52 [A] crystal structure and meets the requirements for pharmacokinetics, pharmacodynamics, as well as toxicity based on studies *in silico* . *Native ligands* is an antagonist that has an antiaging effect. Therefore, ethanol extract of leunca fruit (*Solanum nigrum* L) has antiaging potential. Study This as step beginning for researcher other For continue study *in Vivo* or *in vitro* , so that it can be further developed into a cosmetic product .

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