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Molecular Docking Analysis of *Polyscias scutellaria* Active Compounds as Inhibitor of Dopamine D_2 Receptors to Increase Prolactin Secretion

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Abstract. Shield Aralia (*Polyscias scutellaria*) is one of the plants that grows in Indonesia and has many benefits, especially for health. *P. scutellaria* contains active compounds derivate the flavonoids class. Based on ethnobotany studies, Shield Aralia leaf is widely consumed by nursing mothers with the aim to increase breast milk production. Unfortunately, research related to *P. scutellaria* leaves and their function to increase milk production are rarely done. The aim of this study to determine the potential of active compounds contained in *P. scutellaria* leaves as a dopamine D2 receptor (D2R) inhibitor through molecular docking studies. Based on the results of molecular docking on the D2R protein, it shows the binding value of the drug control affinity (risperidone) -6.9 kcal/mol, afzelin -6.1 kcal/mol, quercetin -6.3 kcal/mol, quercitrin -6.1 kcal/mol, and rutin -7.0 kcal/mol. Inhibitory activity on D2R has an impact on increasing prolactin secretion; thus, it can elevate breast milk production. Based on these results showed that the *P. scutellaria* active compounds can be used as a drug candidate to increase breast milk production.

INTRODUCTION

People have learned the knowledge about the prevention and treatment of diseases from ancient times using plants produced by nature. Society is still applying medicinal plants to treat various diseases to this present time. It is thought that medicinal plants have fewer side-effects than prescription drugs [1], medicinal plants are also cheaper and easier to get [2]. Shield aralia (*Polyscias scutelaria*) is one of the indigenous plants of the Araliaceae family, which have been listed as a medicinal plant and relatively common in Indonesia related to its properties to treat various diseases [3]. *P. scutellaria* or local name "*mangkokan*" is consumed by Indonesian, especially in the form of stew (decoction) [4]. *P. scutellaria* has been reported to have antioxidant, antibacterial activity [3,5], anti-inflammatory [6], and treat breast edema [7]. *P. scutellaria* contains terpenoids, alkaloids, saponins, flavonoids, and polyphenols compounds [5,8,9].

Breastmilk plays a role in infants' nutrition, particularly in protecting infants from various pathogens [10]. Replacing breastmilk with formula milk can raise the risk of several types of diseases in infants, including respiratory disorders and gastrointestinal systems, allergies and obesity [11]. Exclusive breastfeeding for the first 6 months [12] can reduce the risk of neonatal events, mortality in infants and toddlers, and also help postpartum period maternal recovery [11,13]. However, there are several problems that occur during breastfeeding, such as low production of breast milk and causes inadequate nutrition for infants. Insufficient milk production can also lead to breast cancer in women [14]. Low milk production can be caused by several factors, including stress, consumption of certain drugs, smoking, and some issues with the endocrine system [15].

Milk secretion is regulated by various complex hormones during the lactation period. Prolactin is a pituitary gland derived hormone which plays a role in regulating milk production. During pregnancy, secretion of prolactin hormone

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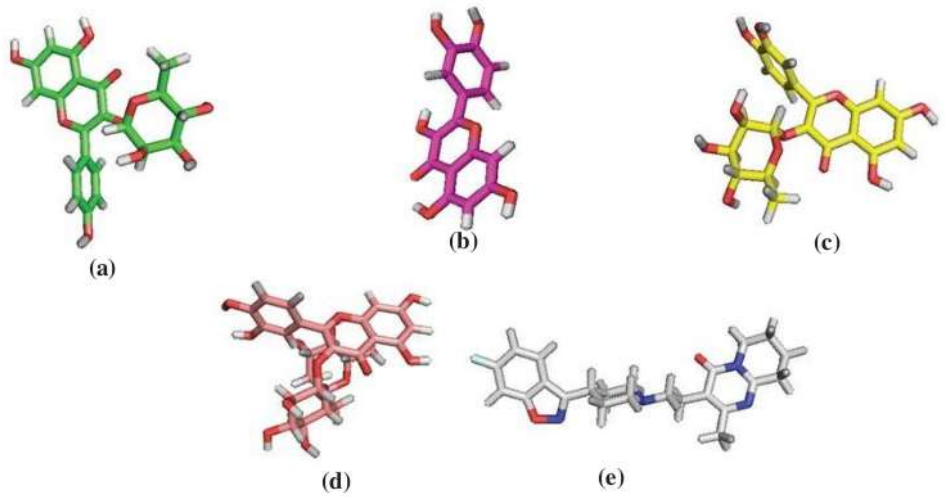
increase [16] and will continue until six weeks after delivery (postpartum) [17]. This causes the expansion and development of the mammary glands. Baby suckling on the breast sends signals from the nipple to the brain and stimulates prolactin secretion. Increased blood prolactin levels may reduce progesterone and estrogen levels, which blocked milk secretion by alveoli cells, and finally, breast milk can be produced [16,18].

Shield aralia leaves have historically been used by the Indonesian to increase breast milk production [7]. However, there were limited scientific studies that reported the benefits of shield aralia leaves as a breast milk booster. This study aims at analyzing the active compounds contained in aqueous leaf extract *P. scutellaria* in the role of increasing breast milk through molecular docking studies.

EXPERIMENTAL DETAILS

Preparation of Ligands and Proteins Target

The 3D chemical structure of the ligands was obtained from the PubChem compound database (https://pubchem.ncbi.nlm.nih.gov/). Ligands that were used in molecular docking were a group of flavonoid compounds found in shield aralia leaves extract, namely afzelin (CID 5316673), quercetin (CID 5280343), quercitrin (CID 5280459), rutin (CID 5280805), and risperidone as drug control inhibitor D2R (CID 5073). The downloaded ligands are in .sdf format and then converted into Protein Data Bank (PDB) used software PyMoL. Target protein Dopamine D2 Receptors (D2R) (ID 6CM4) was obtained from PDB (https://www.rcsb.org/). Water molecules and ligands contained in the target protein were removed using PyMoL software.



GAMBAR 1. Structure of ligands. (a) Afzelin; (b) Quercetin; (c) Quercitrin; (d) Rutin; and (e) Risperidone

Ligand Docking Studies

The interactions between ligands and target proteins were analyzed using AutoDock Vina, which is included in the PyRx 0.8 software [19,20]. The molecular docking site is in X: 40.3573, Y: -8.2393, and Z: 39.3249 and with dimensions X: 6.3276 Å, Y: 9.8300 Å, and Z: 16.6948 Å. Molecular docking was performed on the active site of the target protein. The result of molecular docking was the binding affinity value and ligands interaction. Visualization of docking results using PyMoL and BIOVIA Discovery Studio 2016 software.

RESULTS AND DISCUSSION

Molecular docking is computer-based research using the database to predict the ligands' ability (active compounds) to bind at the active site of the target protein and determine the strength of the binding. [21]. The results of molecular docking between the active compound *P. scutellaria* and Dopamine D2 Receptors (D2R) protein showed that afzelin has the same amino acid residue with risperidone at ALA-1093, and with rutin at ARG-220, ASP-1092, GLN-373, and LYS-370. Afzelin, quercetin, and rutin have the same amino acid residue at ARG-220. Meanwhile, quercetin has the same amino acid residue with risperidone as drug control at ILE-377 and ALA-376. This might suggest that those ligands have the same domain interaction within the target protein based on the similarity of amino acid residues [22].

TABLE 1. Visualization of Docking Result and Ligands Interaction in 2D form of D2R protein with *P. scutellaria* active compounds

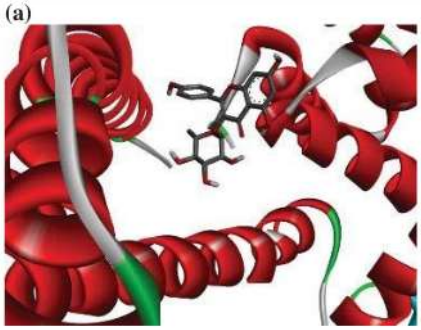
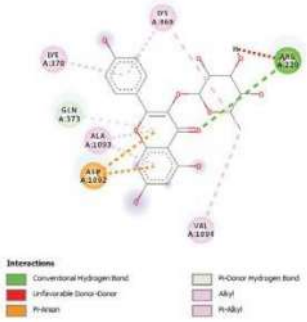
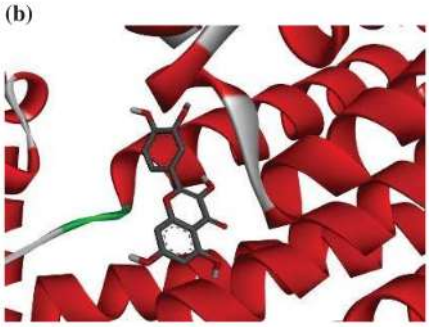
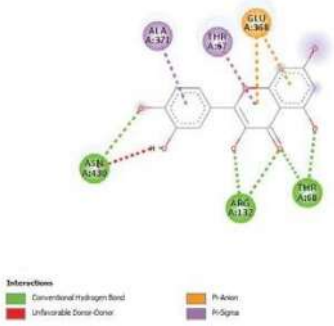
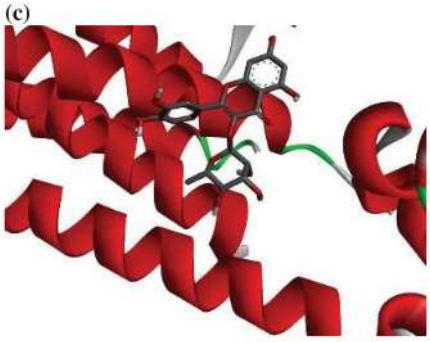
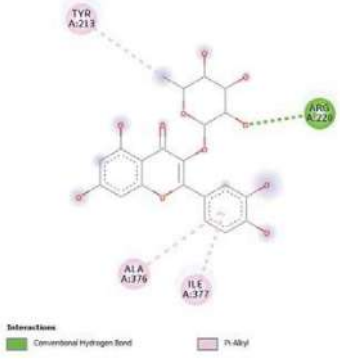
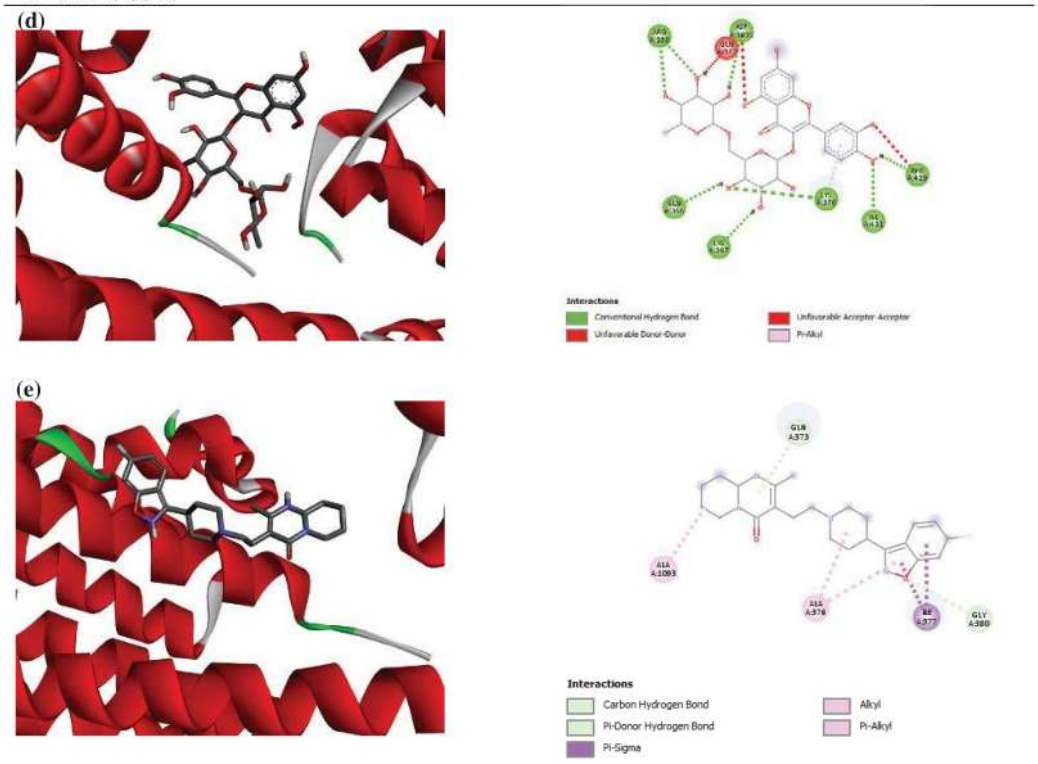
Visualization	Amino Acids Residues
(a) 	
(b) 	
(c) 	

TABLE 1. Cont.



Molecular docking results showed that the binding affinity (Table 2) of the rutin (-7.0 kcal/mol) was more significant than risperidone as a control drug (6.9 kcal/mol). Meanwhile, afzelin, quercetin, and quercitrin compounds have binding affinity values of -6.1, -6.3, and -6.1 kcal/mol, respectively. The smaller binding affinity value indicates that the compound can bind to the target protein more strongly [21,23,24]. Rutin has hydrogen bond into D2R more than other compounds. Hydrogen bond

TABLE 2. Binding affinity value from aqueous leaf extract of *P scutterlaria* with Dopamine D_2 Receptors (D2R)

Ligands	Binding Affinity (kcal/mol)	Amino Acid Residues
Afzelin	-6.1	LYS-369, ARG-220, VAL-1094, ASP-1092, ALA-1093, GLN-373, LYS-370
Quercetin	-6.3	ALA-371, THR-67, GLU-368, THR-68, ARG-132, ASN-430
Quercitrin	-6.1	TYR-213, ARG-220, ILE-377, ALA-376
Rutin	-7.0	ARG-220, GLN-373, ASP-1092, PHE-429, ILE-431, LYS-370, LYS-367, GLN-366
Risperidone	-6.9	GLN-383, GLY-380, ILE-377, ALA-376, ALA 1093

Prolactin is a polypeptide hormone synthesized and secreted by lactotroph cells found in the anterior pituitary gland [25]. Prolactin secretion is dynamic since it is regulated by various hormone and neurotransmitter complexes. Dopamine is a catecholaminergic neurotransmitter that is produced by the hypothalamus and involved in various functions and biochemical activities in the body, such as inhibiting prolactin secretion [26,27]. Dopamine via D2

Receptors (D2R) inhibits the proliferation and activity of lactotroph cells to secrete prolactin. Activation of D2R can suppress prolactin gene expression and inhibit prolactin secretion by lactotroph cells [25,28,29]. Risperidone is an antipsychotic drug used for schizophrenia[30], bipolar disorder, and dementia [31]. Risperidone is also used to boost breast milk production [32]. Risperidone was reported to increase prolactin levels through D2R blocking [30,31]. However, the consumption of antipsychotic drugs may have a negative impact on infants [33].

Galactogogues are plants commonly used to increase breast milk production [34]. Based on the screening reports on various plant species, galactogogues plants typically have terpenoids, flavonoids, tannins, and essential oils as active compounds [35–37]. The active compounds found in aqueous *P. scutellaria* leaf extract include afzelin, quercetin, quercitrin, and rutin are compounds of the family of flavonoids that have antioxidant, antibacterial, anti-inflammatory, anti-cancer, and treat cardiovascular disease[38–40]. Results of molecular docking have shown that the compounds in aqueous *P. scutellaria* leaf extract can bind to the D2R target protein stronger than risperidone. The mechanism of increasing breast milk production through bind with the D2R protein by flavonoid groups found in *P. scutellaria* leaves extract. The blocking of the D2R protein can increase prolactin secretion, thus increase breast milk production in nursing mothers [41].

SUMMARY

Molecular docking studies show that active compounds found in aqueous *P. scutellaria* leaf extract can bind to dopamine D2 receptors and increase prolactin production. This suggested that for breastfeeding mothers, the active compounds in *P. scutellaria* leaves can be used as a candidate for breast milk boosters.

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