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FULL PAPER

# Insilico study of stigmasterol extracted from *pluchea indica* as antiferility in men

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Docking is a method to predict the strength of the interaction between the receptor and the ligand based on the binding affinity value. The docking carried out in this study is a specific docking with a grid box imitating the bond between AR and inhibitor control drugs. This study aimed to investigate stigmasterol from beluntas leaves potential molecularly as antifertility in men. This type of research is descriptive and exploratory. The research was carried out from November to December 2019. The research was carried out with the help of Indonesia's Bioinformatics and Biomolecular Analysis Organization (INBIO). Method of analysis with 3 steps: (1) Looking for a collection of metabolites and pass online, (2) molecular docking and MD simulation, and (3) drug-likeness and toxicity. Determination of compound potency based on binding affinity value. The more negative the binding affinity, the stronger the interaction between the receptor and the ligand. The results showed that it was predicted that stigmasterol could attach to the same active site (of Methyltrienolone) as the control to affect AR. Stigmasterol has a binding affinity value close to that of the inhibitor control, which is -5.4 kcal/mol, while the inhibitory control has a binding affinity value of -4.6 kcal/mol. The ideal value for control is -7 kcal/mol. The results of the MD Simulation analysis found that the AR-Stigmasterol complex was more stable than the AR-Cyproterone acetate complex due to its lower RMSD and RMSF values. The finding of this study confirmed that stigmasterol from beluntas leaves has the potential as an antifertility for men.

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## Introduction

The government proclaimed the Family Planning Program (KB) as a national program, along with the increasing population densities in various countries. Based on data from the BKKBN (2012), population density in Indonesia is a problem that develops complexity every year. Efforts to regulate fertility through contraception and infertility management are essential components of reproductive health [1,2].

Family Planning Programs (KB) for men are still in minimal demand due to many factors, including few and very limited choices and knowledge of the safety requirements that are still low [3,4]. Current male contraceptive methods include periodic abstinence, condoms, interrupted intercourse, and vasectomy [5,6]. An attempt to find a male

contraceptive method that is acceptable and meets the safety requirements is one of the main steps to increase the role of men in Family Planning Programs (KB) [7,8].

Until now, there is no utterly ideal method of contraception [9]. The choice of contraception must meet certain conditions to be accepted by society, especially men. The security requirements should be fulfilled, including reliability, harmless, widely accepted, safe, easy to obtain, and have minor side effects [10,11].

Plant secondary metabolites are one of the beneficial compounds used to treat many diseases nowadays. Many potential compounds from a plant have antifertility potential. Stigmasterol from beluntas leaves is one example. Stigmasterol is a group of phytosterol, a derivative of the steroid compound [12]. Since the 1990s, phytosterol has been commercialized as nutraceuticals or drugs [13]. Compounds like alkaloids, triterpenoids, steroids, flavonoids, tannins, saponins, and stigmasterol in plants, should be considered to test for their antifertility potential [14,15].

Stigmasterol should be studied further to investigate how this compound work and its potential for certain diseases [16]. Molecular biology is the science that studies related molecular interactions in living things, especially cells, including deoxyribonucleic acid, ribonucleic acid, and protein. Utilizing technology and bioinformatics studies is constructive in providing information about the visualization and position of a compound and its interaction with receptors [17,18].

Docking is a method for predicting the strength of the interaction between receptors and ligands based on the binding affinity value. Docking has been widely used by pharmaceutical companies in drug discovery, so docking is one of the relevant analyses for predicting an interaction of compounds with receptors in research looking for antifertility compounds [19,20]. This study investigated stigmasterol compounds in beluntas leaves molecularly as antifertility in men.

## Martials and methods

The research type is descriptive, exploratory, and carried out from November to December 2019. Data retrieval of this research is conducted by the help of Indonesia's Bioinformatics and Biomolecular Analysis Organization (INBIO). The analytical method with the initial step is Metabolite collection and Pass Online; Stigmasterol was obtained from the previous study (Kanaya Database), while the 3D structure and SMILE (*simplified molecular-input line-entry system*) obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/).

Way2Drug PASS Online (http://www.pharmaexpert.ru/passonline) is a web tool used to determine the compound's bioactivities based on its structural similarity with one proven as a contraceptive. The more similar the structure of the input compound (stigmasterol) to the database data, the higher the predictive value.

The second step is *molecular docking* using autodock vina in the PyRx 9.5 program. The protein used as the target was *Human Androgen Receptor* (AR) Chain A (PDB ID 1E3G), while the control inhibitor used was Cyproterone acetate (antagonist). Docking is carried out specifically with the site on the Methyltrienolone active site [21-24]. The SDF ligand's 3D structure was obtained from the PubChem database. The PyMol 2.3.1 program is used for 3D visualization of the docking results, while the LigPlot 2.1 program visualizes the 2D interactions of amino acids. The complex generated in this stage was then brought forward to test its stability, known as *MD Simulation*, using *the web tool* Simlab (https://simlab.uams.edu/). This analysis will obtain data regarding the value of *Root Mean Square Deviation* (RMSD) and *Root Mean Square Fluctuation* (RMSF). The data will

be used as the basis of analysis to determine the stability of the resulting complex [25-28].

The third step is *drug-likeness* and toxicity prediction. The analysis scope called ADME (*Absorption, Distribution, Metabolism,* and *Excretion*) is an analysis to determine the pharmacokinetics of the drug. The admetSAR (lmmd.ecust.edu.cn/) web tool is used for this prediction stage. The result analysis used the comparison with Lipinski parameters. *Lipinski's rule of 5* has the following criteria: (a) Not more than five hydrogen bond donors (the total number of nitrogen–hydrogen and oxygen-hydrogen bonds), (b). No more than ten hydrogen bond acceptors (all nitrogen or oxygen atoms), (c) The molecular weight is less than 500 daltons, and (d) LogP not more than 5 [29-32].

*The blood-brain barrier* (BBB) is an analysis to predict whether the compound can penetrate the blood-brain barrier. In contrast, HIA (*Human Intestinal Absorption*) is a prediction to estimate the number of compounds absorbed by the *Gastrointestinal* (GI). With higher HIA value, the compound is more absorbed (not discussed in the results, but attached to the Excel data). Stigmasterol is a compound that passes the drug-likeness Lipinski rule of 5. The results were analysed descriptively [33,34].

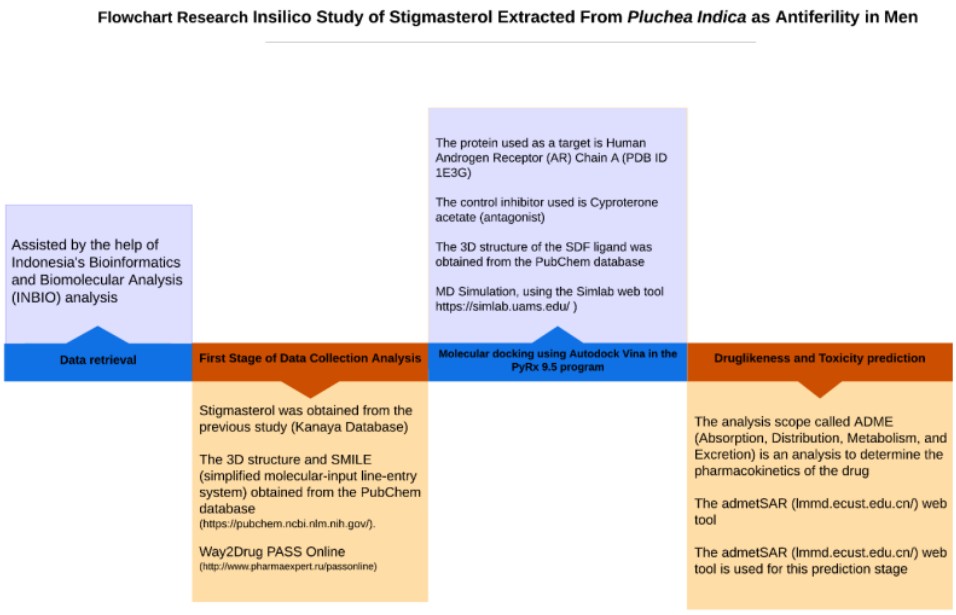


**FIGURE 1** Flowchart research

## Results and discussion

The results of this study include some data based on research steps, including the Pass server and *Molecular Docking* results. Pass Server results when screened using other molecules contained in *Pluchea indica*. Several compounds are potential candidates for contraception in men. The potential of the active compounds in *Pluchea indica* was reviewed based on the predicted Pa (*Probability to be Active*) value with the Way2Drug PASS Online server (http://www.pharmaexpert.ru/passonline) through the similarity of the bioactive structure with the potential recorded in *the database*. *Probability Active to be (Pa*) is a value that describes the potential of the

compound being tested. The parameters used are as follows: (1) When the Pa value is more than 0.7, it indicates a high similarity with the compound in the database that has been proven to have the same activity, (2) if the Pa value ranges from 0.3 to 0.7, it indicates a low similarity to the compound in the database [35,36]. Prediction results of analysis of bioactive compounds contained in beluntas leaf extract are presented in Table 1.

**TABLE 1** Prediction of bioactive *Pluchea Indica* based on Pa Pass Online value

| Compound | Apoptosis Agonist | Contraceptive | Testosterone 17 beta-dehydrogenase (NADP+) inhibitor |
|---|---|---|---|
| Stigmasterol | 0.752 | 0.572 | 0.915 |

Studies of male contraception generally focus on sperm quality. Apoptosis is a useful index to see sperm quality. Apoptosis can affect sperm concentration and affect fertility [37]. Meanwhile, 17 beta-dehydrogenase (17 beta-HSD-3) is an essential enzyme in testosterone biosynthesis. Androstenedione, a testosterone precursor, is converted into testosterone using the 17-beta-HSD-3 enzyme (Uniprot and Brenda Database). Unfortunately, the tannin compound cannot undergo the prediction test due to its size being too large. Based on the Pass results, Stigmasterol is a compound that has the potential as a candidate for contraception in men.

The result of the second analysis is molecular docking. Docking carried out in this study is a specific docking with a grid box imitating the bond between AR and control inhibitor drugs. Docking is a method to predict the strength of the interaction between the receptor and the ligand based on the binding affinity value. The negative the value, the stronger the interaction between the receptor and the ligand. If the tested bioactive has a score close to the control score, indicating the compound has the ability as an Androgen Receptor (AR) inhibitor [38-39]. Sertoli cells need the Androgen Receptors (AR) for haploid spermatid differentiation [40]. The AR in Leydig cells and peritubular myoid cells plays an essential role in spermatogenesis. Therefore, AR inhibition is one way to control fertility and spermatogenesis. The results of docking bioactive with PyRx 9.5 are listed in Table 2.

**TABLE 2** Docking result of boactive using PyRx 9.5

| Receptor | Ligand | PubChem ID | Binding Affinity (kcal/mol) |
|---|---|---|---|
| Androgen Receptor (AR) | Methytrienolone | PDB ID 1E3G | -6.1 |
| | Stigmasterol | 5280794 | -5.4 |
| | Cyproterone acetate (antagonist) | 9880 | -4.6 |

The docking results indicated that it was predictable that stigmasterol could attach to the same active site (from Methytrienolone) as the control to affect the Androgen Receptor (AR). Stigmasterol has a value that is close to the control inhibitor, which is -5.4 kcal/mol, while the control inhibitor is -4.6 kcal/mol. The ideal value for control is -7 kcal/mol [41-42]. Visualization of the docking results and the position of stigmasterol attachment to the active site of Methyltrienolone and its ability to affect AR are displayed in Figure 1.

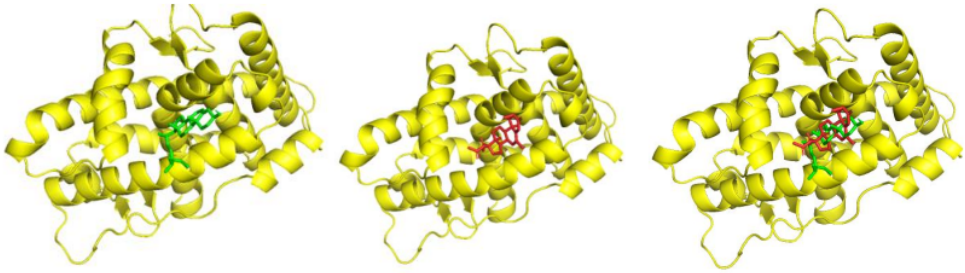

**FIGURE 2** Docking Result Visualization of AR, Red (control) and Green (Stigmasterol).

**TABLE 3** Amino acids interaction using LigPlot analysis

| Compound | Hidrogen Bond | Hidrofobik Bond |
|---|---|---|
| Cyproterone acetate | GLN738 (3.13) | VAL730 LYS720 VAL716 MET894 MET734 |
| Stigmasterol | GLN733 (3,35) | VAL716 VAL713 MET894 VAL730 LYS720 MET734 ILE737 |

*Highlights* represent the identical amino acid residues between the control and comparison ligands. Hydrophobic bonds in the image are visualized in black font, while hydrogen bonds are in green font. The number in brackets is the bond distance in Angstroms. The visualization of interaction results of amino acids with ligPlot is depicted in Figure 2.

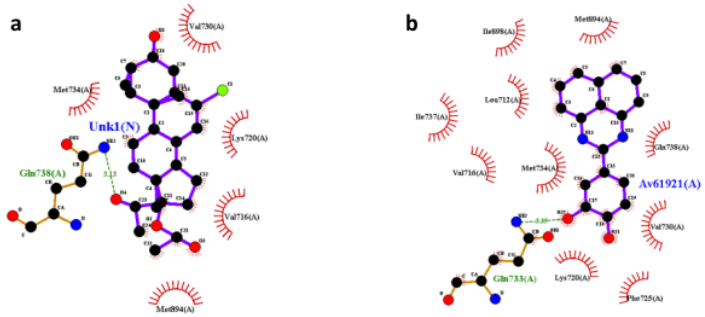


**FIGURE 3** Visualization of amino acids interaction using LigPlot. (a) Cyproterone acetate and (b) Stigmasterol.

Figure 3 shows the interaction of amino acids with LigPlot, indicating that Cyproterone acetate binds to the amino acid GLN at position 738 on the AR.. The type of bond that occurs is a hydrogen bond with a bond distance of 3.13 Angstrom with a hydrophobic bond VAL730 LYS720 VAL716 MET894 MET734. Stigmasterol binds to the Human Androgen Receptor (AR) on the amino acid GLN number 733. The type of bond that occurs is a hydrogen bond with a bond distance of 3.35 Angstrom with a hydrophobic bond VAL716, VAL713, MET894, VAL730, LYS720 MET734, and ILE737.

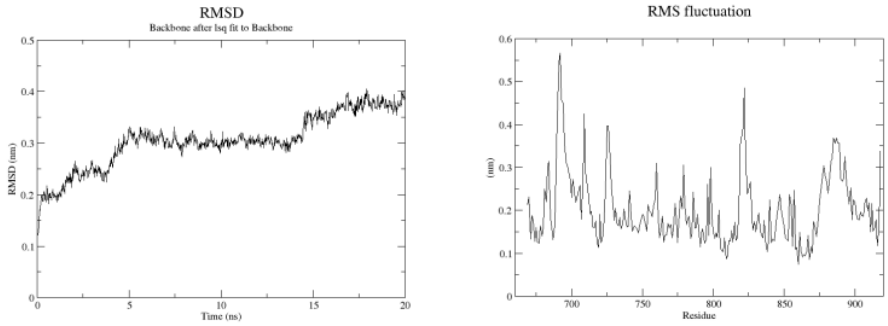


**FIGURE 4** MD simulation graph of AR-Cyprosteron acetate complex

Based on the results of the *MD Simulation*, the graph in Figure 4 shows the RMSD and RMSF values of the *AR-Cyproterone acetate*. The RMSD graph shows a score of 0.31 nm (3.1 Å). The RMSD score of a complex exceeds 0.3 nm (3 Å), and then the complex is said to be less stable. The graph shows that in the first five ns, a steep graph is formed; this is due to the initiation process of interactions between macromolecules and ligands. After that, a stable graph is formed at the following five ns, indicating the interaction has entered a stable stage, but at the next 15 ns, the graph shows an increase. The changes in the graph indicate that the interaction distance between the macromolecules and the existing ligands is increasing [43-45]. This event implies an increased conformational change of this macromolecule interacting with the *Cyproterone acetate*.

In the RMSF graph, the amino acid residues interacting with macromolecules show a relatively high RMSF score but are still below the minimum score of 0.25 nm/2.5 Å. The respective scores obtained were GLN738 (0.25 nm/2.5 Å), VAL716 (0.18 nm/1.8 Å), VAL730 (0.2 nm/2 Å), LYS720 (0.19 nm/1.9 Å), MET734 (0.2 nm/2 Å), and MET894 (0.25 nm/2.5 Å). If the RMSF score exceeds 0.25 nm/2.5 Å, the level of fluctuation is high, causing the resulting complex to be unstable. Based on the data, some residues have high fluctuations up to 0.25 nm/2.5 Å. As seen in the previous RMSD graph, at the next 15 ns, there is an increase in the interaction distance between the ligands and macromolecules. The scene occurs because the fluctuating levels of amino acid residues that interact with the ligands are high. Therefore, a conformational change in the complex occurs [45,46]. The RMSD and RMSF analysis of the *AR-Cyproterone acetate* complex showed that this complex was not very stable.

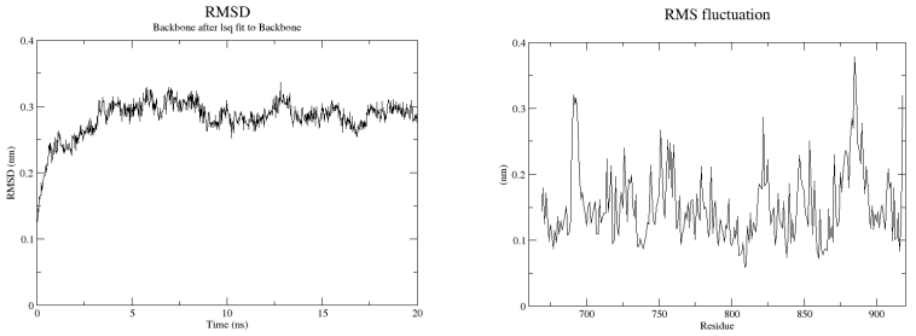


**FIGURE 5** MD simulation graph of AR-Stigmasterol complex

Based on the RMSD plot shown in Figure 5, it can be observed that from 0 to 5 ns, there is a steep curve indicating an early-stage binding interaction between the AR protein and stigmasterol in the simulation. After this situation occurs, the complex will show a stable graph in the next second [38]. At the next five ns seconds, the complex has entered a stable stage so that the resulting graph does not show a steep change; the resulting RMSD value determines the complex's stability. If the value is below 0.3 nm/3 Å, it is classified as a stable interaction [47]. As in the RMSD graph above, the RMSD value obtained is 0.29 nm/2.9 Å, indicating that the complex's conformational change is small. When the conformational change is high, indicating an easily separated ligand from the macromolecule [48].

The second graph shown in Figure 5 displays the RMSF plot. RMSF values below 0.25 nm/2.5 Å indicate a stable complex due to low fluctuation levels. In the graph above, it can be seen that the active residues of macromolecules that interact with ligands show low values, namely ILE737 (0.15 nm/ 1.5 Å), VAL713 (0.13 nm/ 1.3 Å), VAL730 (0.15 nm/ 1.5 Å), LYS720 (0.1 nm/ 1 Å), VAL716 (0.14 nm/ 1.4 Å), MET894 (0.13 nm/ 1.3 Å), and MET734 (0.14 nm/ 1.4 Å) [49-50]. These residues have fluctuation levels below 0.25 nm/ 2.5 Å. Therefore, the bond interactions between macromolecules and ligands have integrity and rigidity [51]. Based on the results of this analysis, the AR-Stigmasterol complex is solid and stable.

Stigmasterol is a plant compound with an antifertility effect. Stigmasterol plays a role in the metabolic process of the hormone's progesterone, androgens, estrogens, and corticoids [52-53]. Androgen and estrogen play a role in the process of spermatogenesis. Stigmasterol (β-sitosterol) from the Barleria root caused changes in the male reproductive depicted by the reduced level of testosterone, FSH, LH, sperm motility, and sperm density [54]. These effects lead to the suppression of spermatogenesis, resulting in infertility in white male rats and male experimental animals. Plants with steroid derivatives like diosgenin, hecogenin, and stigmasterol could be antifertility. The result of these various traits is a decrease in the number of births [55].

The working principle of stigmasterol is that it is cytotoxic and interferes with the hormonal system. Steroid-active ingredients like stigmasterol were essential for making steroid hormones. This steroid hormone could disrupt the balance of gonadotropin hormones [56]. The higher the concentration of a formulation, the higher the active ingredients

contained [57]. The active substance can affect the work of hormones and cell metabolism. Cell damage can occur due to cytotoxic effects that cause hormonal disturbances. Stigmasterol in beluntas leaves has a steroid chemical structure. Steroids are the basic structure of the testosterone hormone. The mechanism of action of the active compound enters through the biosynthesis of steroids, especially testosterone, so a material structurally similar to testosterone will be produced [58].

Testosterone harms the anterior pituitary gland as an amplifier of the anterior pituitary negative feedback on the hypothalamus. This negative feedback inhibits LH synthesis and secretion, and also decreases testosterone secretion. The testosterone that can cause this kind of feedback is free testosterone. Free testosterone can passively enter the target organ (Sertoli cells) through diffusion. The free testosterone is transformed into a more active product, dihydrotestosterone (DHT). The conversion of testosterone to dihydrotestosterone is catalysed by the enzyme 5α-reductase. This DHT will cause the release of a certain protein (Hsp 90) from the androgen receptor, allowing DHT to bind to the androgen receptor found in the cytoplasm of the Sertoli cells [59-60].

The DHT-receptor complex will enter the cell nucleus and interact with specific sequences of Sertoli cell DNA. This attachment will induce the mRNA synthesis. The DHT-androgen receptor-DNA complex, RNA polymerase, and basal transcriptional proteins will initiate protein synthesis, eventually forming *androgen-dependent proteins*. Proteins synthesized in Sertoli cells are needed for the division/meiosis of spermatogonia. Spermatogenesis can occur if the pituitary-gonadal functional-gonadotropin relationship normally runs [61-62].

## Conclusion

Molecular docking showed that the binding affinity score for the AR-Stigmasterol complex was -5.4 kcal/ mol, which is higher than the AR-Cyprosteron acetate complex, with a score of -4.6 kcal/ mol. The MD simulation stability test showed that the RMSD and RMSF values of the AR-Stigmasterol complex were classified as solid and stable compared to the AR-Cyprosteron acetate complex. ADMET prediction also shows that stigmasterol did not violate Lipinski's Rule of Five. Hence, it is safe and consumable. The good binding affinity results, stable interaction of the AR-Stigmasterol complex and ADMET analysis confirmed that stigmasterol has the potential to antifertility for men.

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## Conflict of Interest

The authors declare that there is no conflict of interest.

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