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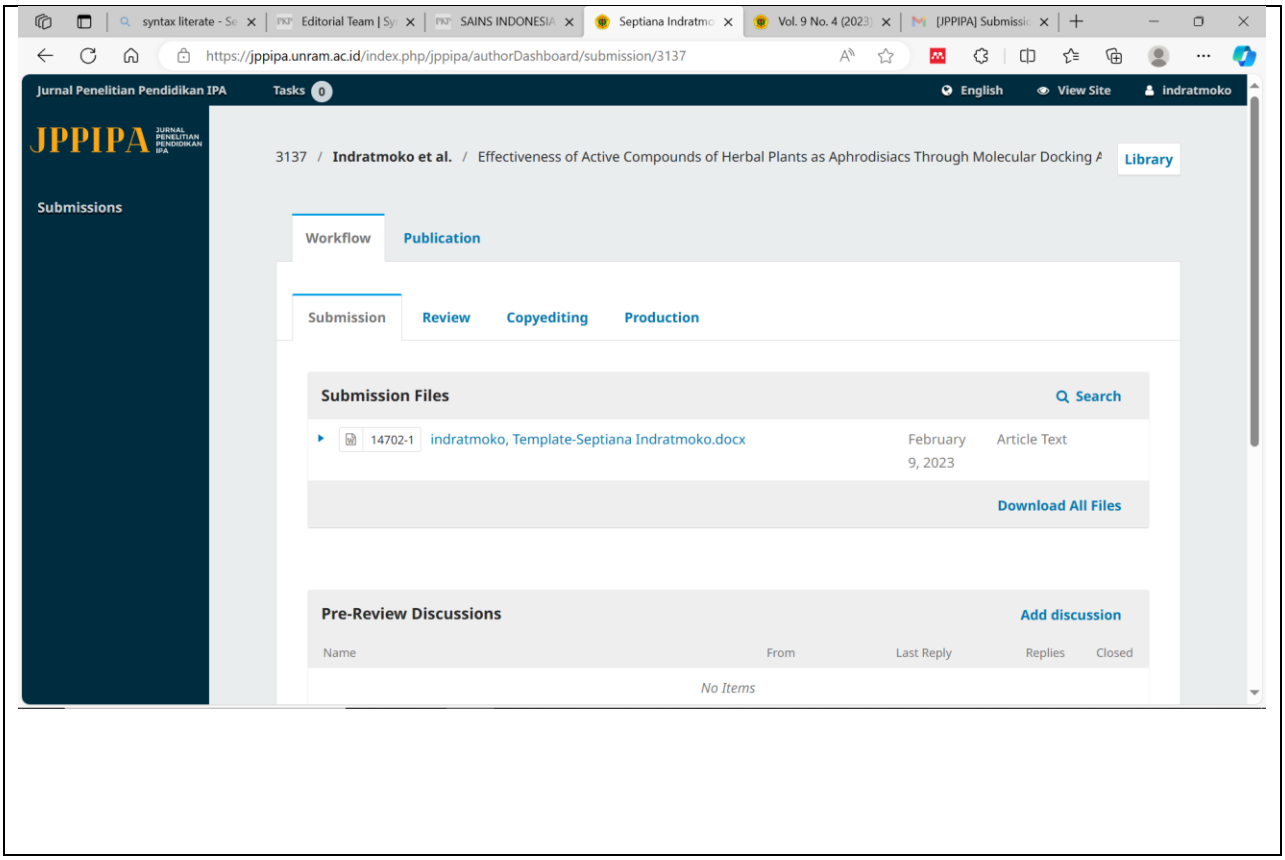

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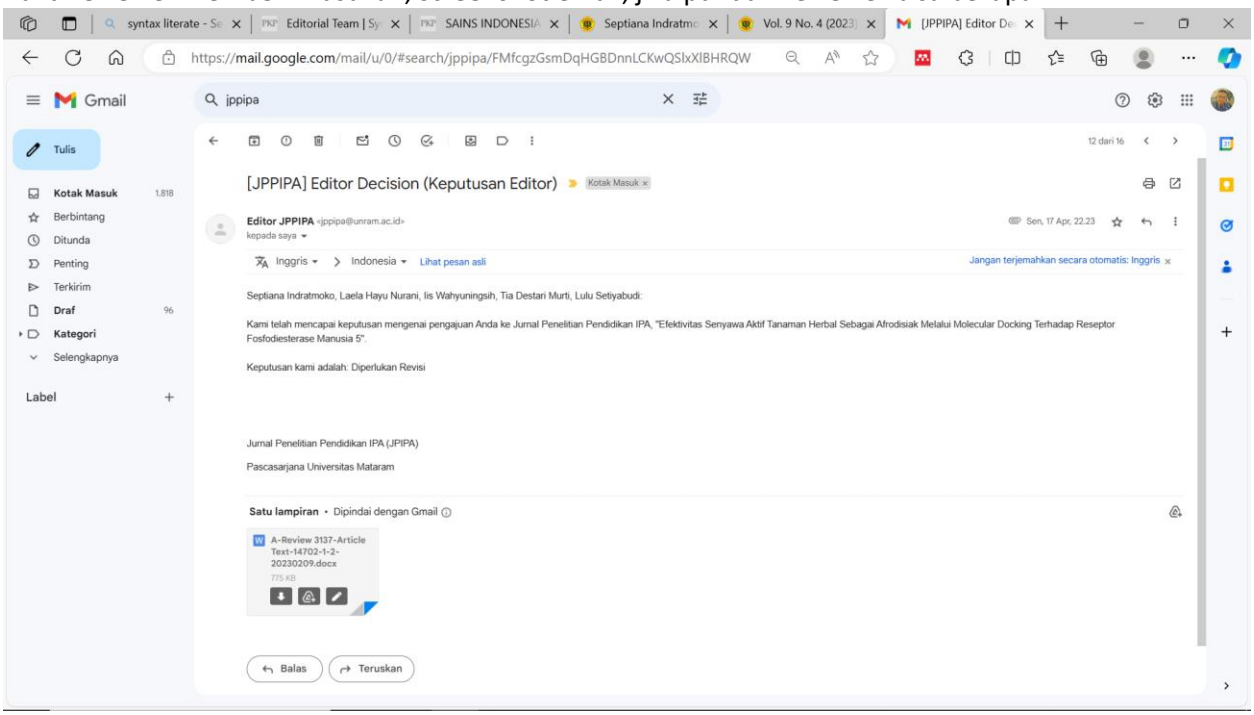

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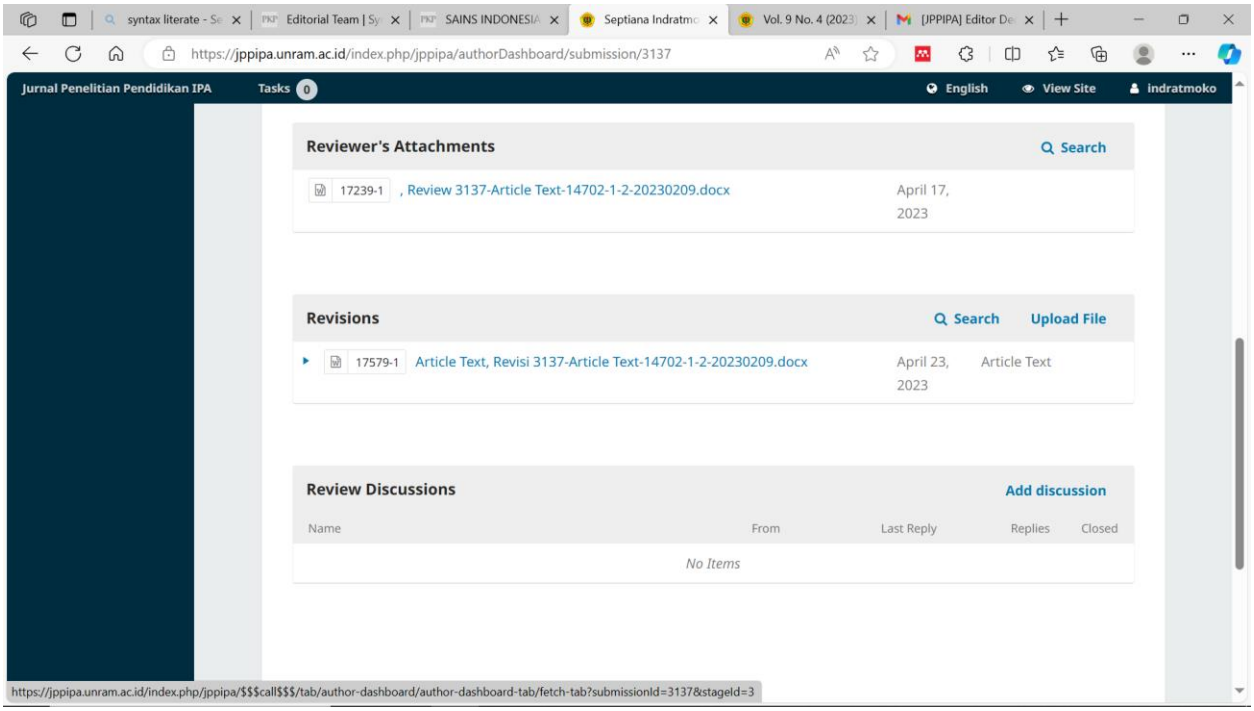

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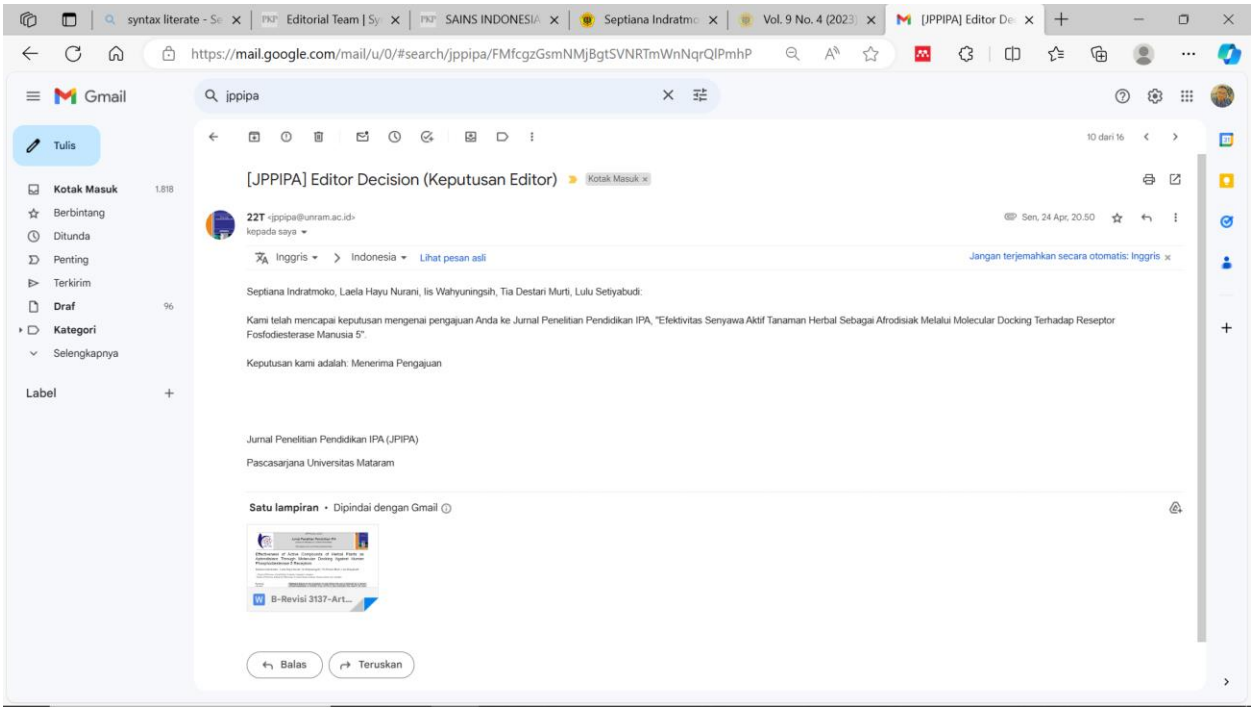

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Effectiveness of Active Compounds of Herbal Plants as Aphrodisiacs Through Molecular Docking Against Human Phosphodiesterase Receptors 5

Septiana Indratmoko[1, 2, *], Laela Hayu Nurani[1], Iis Wahyuningsih[1], Tia Destari Murti[2], Lulu Setiyabudi[2]

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Abstract: Based on the evaluation of side effects the use of sildenafil as a human phosphodiesterase 5 inhibitor drug (HPDE5) has prompted the search for new compounds that have the potential to be aphrodisiacs. The purpose of this study was to determine the interaction of the active compounds nilocitin, stigmasterol, protodioscin, icariin, yohimbine, and ginsenoside against the HPDE5 receptor as an aphrodisiac. The method used in this study was experimental conducted in silico. The metabolite structure is downloaded from the PubChem application, the protein is downloaded from PDB (Protein Data Bank) with the code 2H42. The result of this study is that the active compound may interact with HPDE5 receptors. The interaction that occurs results in the formation of van der waals bonds, hydrogen, carbon hydrogen, sigma, sulfur cation anions, T-shape and alkyls. The active compounds each have a sildenafil bond energy of -9.5 kcal/mol; niloticin -7.8 kcal/mol; stigmasterol -10.7 kcal/mol; protodioscin -13.1 kcal/mol; icariin -11.1 kcal/mol; yohimbine -10.1 kcal/mol and ginsenoside -12.1 kcal/mol with RMSD 0. The interaction with the HPDE5 receptor results in the formation of the same amino acid residue as the comparison ligand. The residual equation shows that the compounds have the same activity and can be predicted as aphrodisiacs.

Keywords: *Aphrodisiac herbs, Erectile dysfunction, Human phosphodiesterase 5, In silico*

Introduction

Sexual dysfunction is the inability to achieve satisfactory sexual intercourse in the form of erectile dysfunction (ED), reduced libido, and abnormal ejaculation (Sin, Anand, & Koh, 2020). DE is the sexual dysfunction disorder with the highest prevalence, this state can affect emotional and physical self-esteem, psychosocial conditions such as depression, anxiety, and quality of life disorders(Kazemi et al., 2021) and a significant impact on the quality of life of sufferers (Winarta, Duarsa, & Kandarini, 2020). The prevalence of ED in men aged 40-75 years was 52%, and mild, moderate, and complete DE was 2.17%, 2.25%, and 6.9%, respectively (Maleki-Saghooni, Karimi, Bakhshi, & Abdollahi, 2020). Age is one of the factors that can influence the occurrence of DE, where ED increases with age (Goldstein, Goren, Li, Tang, & Hassan, 2020).

DE that cannot be cured with lifestyle changes, requires support with therapies such as Human Phosphodiesterase 5 inhibitors (HPDE5) (Raheem et al., 2021). HPDE5 inhibitors are the second-line treatment for ED after behavior modification, since this drug is of the nature of only helping to improve the quality of

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erections for men by increasing blood flow in the corpora cavernosa (Ganapathy, Priya, & Kumaran, 2020).

PDE5 is one of the enzymes that plays a key role in regulating many cGMP-mediated physiological processes, so HPDE5 inhibitors are the target of various health disorders such as erectile dysfunction, pulmonary and cardiovascular hypertension (Ahmed, Geethakumari, & Biswas, 2021) (Isidori et al., 2021). Based on the evaluation of side effects occurring from the use of synthetic drug inhibitors HPDE5 has prompted the search for new compounds that have the potential to be aphrodisiacs. Natural aphrodisiac active compounds usually come from the flavonoid group, alkaloids, and also steroid saponins (Gunawan, 2020).

Some active compounds that are thought to have aphrodisiac activity are niloticin from the Eurycoma longifolia plant (*Eurycoma longifolia Jack*.) (Hadi, Anwar, Khairunnisa, & Komari, 2020), stigmasterol from purwoceng plant (*Pimpinella alpina Molk*) (Abdullah & Wibowo, 2021), protodioscin from rujak polo plant (*Tribulus terrestris*) (Maleki-Saghooni et al., 2020), Icariin from goat horn grass plants (*Epimedium sp.*) (Ganapathy et al., 2020), Yohimbine from yohimbe (*Pausinystalia johimbe*) plant (Brunetti, Lo Faro, Tini, Busardò, & Carlier, 2020) and ginsenoside from chinese ginseng plant (*Panax ginseng Mayer*) (Lin, Xie, Zhong, Huang, & Shi, 2022).

Along with the times, the discovery or development of new drugs is now easier to do so that in new drug planning begins to limit the treatment of test animals because it takes time and costs a lot and a code of ethics is needed for the use of test animals. Therefore, in silico began to be looked at because of its cheap advantages and faster results. In silico is a research method that utilizes computing technology and databases to develop further research (Makatita, Wardhani, & Nuraini, 2020). The in-silico method is a computer-based research study. The use of the in silico method has been used to predict the pharmacological effects of compounds on the target genes studied (Bare, Helvina, Elizabeth, & Sari, 2019) and played a role in the design and discovery of bioactive compounds in the drug development process (Kesuma, Siswandono, Purwanto, & Hardjono, 2018).

In this study, molecular docking will be carried out using the in silico method, ligand and protein structures downloaded from the Protein Data Bank database and then molecular tethering is carried out using PyRx software and BIOVIA Discovery Studio to determine the interaction and affinity of the bond energy so that the chemical content of the active ingredient in the plant can be used as the basis for drug discovery that is predicted to have the strongest potential as a natural aphrodisiac candidate.

Method

This research is a type of experimental research using the in-silico method. This research will carry out the molecular docking process of the compounds niloticin, stigmasterol, protodioscin, icariin, yohimbine and ginsenoside against the HPDE5 receptor to determine its interaction as an aphrodisiac. The tests carried out are ligand and receptor preparation, ligand and receptor preparation, validation, molecular molecular docking using Pyrx-Autodock Vina and visualization with BIOVIA Discovery Studio Visualizer.

Tool

The tools used in this study are hardware in the form of an Asus-X441M Laptop with an Intel® inside™ N-4000 CPU @2.6 GHz processor, 4.00 GB of RAM. The software used is Pyrx-Autodock and Vina, and BIOVIA Discovery Studio.

Material

The ingredients used in in silico research are the structure of natural compounds that have the potential to be aphrodisiacs, namely niloticin, stigmasterol, protodioscin, icariin, yohimbine and ginsenoside and the chemical compound sildenafil (PDE5 inhibitor) downloaded in the Pubchem application database (https://pubchem.ncbi.nlm.nih.gov/). HPDE5 receptors downloaded in the Protein Data Bank (https://www.rcsb.org/).

Research Procedure

Ligan Preparation

The ligands to be used are niloticin compounds, stigmasterol, protodioscin, icariin, yohimbine and ginsenoside and sildenafil chemical compounds downloaded in the Pubchem database in the form of 3D conformation with SDF format.

Preparasi Reseptor

Receptor preparation is carried out by downloading PDE5 in the Protein Data Bank with PDB format. The protein is cleaned from water molecules so as not to interfere at the time of docking simulation. If the receptors are clean then polar hydrogen is added to the chemistry>>hydrogen>>add>>polar only>>ok options. The ligand and receptor structure is then opened with the application of Pyrx- AutoDock first to prepare the ligands and receptors, the stages are as follows: added ligands and receptors of PDB format in the applicationPyrx- AutoDock then select the ligand file and convert to pdbqt. Furthermore, the receptors and receptors will be displayed in PDBQT format.

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Validasion

The molecular docking validation process is carried out using the Pyrx-vina application by preparing a place where ligands will inhibit the receptor by arranging the gridbox on the active side of the receptor or by covering the entire molecule. Adjust the gridbox at the specified coordinates (center x, y, z).

Molecular docking of niloticin, stigmasterol, protodioscin, icariin, yohimbine and ginsenoside compounds in human phosphodiesterase 5

The Pyrx application is run using vinawizard and waited until the running process is complete. After the molecular docking is completed, the binding results of the ligands studied will appear. Save the dataexcel containing the energy value of its bond and save the result of docking between the ligandand receptors in PDB format.

Visualization of the Structure

The last stage in the molecular docking process is visualization. The docking results with the best conformation were then analyzed using Discovery Studio and then viewed the results in 2D and 3D form.

Test Lipinski's Rule of Five

The steps to test plant chemical compounds, first open the website http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp then the chemical structure of the compound in 3D form in the form of PDB is inputted at the normal pH value (7) and finally click submit.

Result and Discussion

Ligan Preparation

The initial stage of the study is to conduct a search for ligands. The ligands tested in this study are compounds that are predicted to have activity as an aphrodisiac. These compounds include niloticin, stigmasterol, protodioscin, icariin, yohimbine and ginsenoside. The ligands to be tested are obtained or downloaded in 3D conformation form in SDF format from the PubChem database. The prepared ligands are prepared, namely by changing the ligand format of the SDF into the form of a Protein Data Bank (PDB) so that molecular molecular docking can be carried out.

Sildenafil is the first active ingredient used as a peroral DE disorder therapy, working through inhibition of Phosphodiesterase 5 (PDE5) approved by the Food and Drug Administration (FDA) for the treatment of DE (Ongaro, Zagotto, Memo, Gianoncelli, & Ribaudo, 2021). In this study, sildenafil functioned as a comparison ligand. Sildenafil is downloaded from the PubChem database in the form of a 3D conformer with SDF format which is then prepared ligands by converting the format into the form of a Protein Data Bank (PDB).

Luteinizing Hormone is a glycoprotein hormone associated with follicle-stimulating and thyroid-stimulating hormone. Luteinizing hormone is very important in human reproduction and is a hormone that plays an important role in being used as the basis for drug discovery for endocrine diseases (Duan et al., 2021). Luteinizing hormone in this study was used as a native ligand or natural ligand from the body downloaded from the Protein Data Bank (PDB) with the code 7FIJ. This hormone is in the form of proteins or macromolecules so that molecular docking cannot be done against the HPDE5 receptor because the pyrx application is not compatible with docking between proteins.

Receptor Preparation

The macromolecule that will be used in the molecular docking process is Human Phosphodiesterase 5 (HPDE5). Optimization is carried out by removing solvent molecules or solvents, namely water. This is so as not to interfere with the molecular molecular docking process. After the removal of water molecules, the addition of hydrogen atoms is necessary because the presence of hydrogen atoms can affect the results of molecular interactions. After ligand separation and optimization, the results of PDE5 macromolecules are stored in the form of PDB files. The results of receptor preparation are shown in figure 1.

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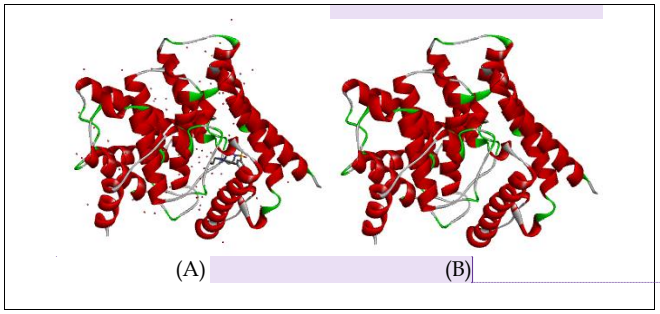

Figure 1. HPDE5 Receptor Preparation Results, (A) before preparation, (B) after preparation Validasi

Validation is carried out in the absence of water because it will block ligand bonds with its receptors because water can form hydrogen bonds with receptors (Ruswanto et al., 2018). Validation of molecular docking is done with the gridbox settings. Gridboxes are the sides of the area to be shot, where the smaller the gridbox, the hope is that the more precise it will be and the results obtained will be more accurate. The gridbox is set on the active side of the receptor or by covering the entire part of the molecule so that the ligand can place where it will inhibit the receptor. The gridbox is adjusted at center coordinates x = 22.4305; y = 126.2819; and z = 13.9905 and at dimensions x = 62.6329, y = 58.9924, and z = 61.1605 Angstrom. Then molecular docking is carried out using Pyrx-Autodock Vina so that a Root Mean Square Deviation is produced. RMSD indicates the distance of atoms in a conformation, the smaller the RMSD value, the better the ligand position because it is close to the conformation of the ligand origin. The value of RMSD depends on the interaction of bonds and energy between proteins and ligands, the smaller the RMSD value, the more similar the structure of the reacted ligand. The rmsd value received is less than two.

Molecular docking

In this study, testing niloticin, stigmasterol, protodioscin, icariin, yohimbine and ginsenoside compounds as well as PDE5 Inhibitors (sildenafil) was carried out by molecular docking these compounds with HPDE5 receptors. The file format of the active compound will be changed automatically in the open babel program, then by doing the same gridbox settings with molecular docking validation, the molecular docking process of the entire test ligand is carried out. The result of molecular docking is the value of RMSD and gibbs free energy (ΔG), as well as ligand conformation with the file format, pdbqt.

Visualization of sildenafil, niloticin, stigmasterol, protodioscin, icariin, yohimbine and ginsenoside against HPDE5 receptors

The interaction between the chemical compound sildenafil and the HPDE5 receptor has carbon hydrogen bond, sigma pi bond, sulfur pi bond, T-Shape pi bond, and alkyl bond. The interaction between the chemical compound niloticin and the HPDE5 receptor no bonds formed. The interaction between the chemical compound stigmasterol and the HPDE5 receptor has a hydrogen bond and alkyl bond. The interaction between the chemical compound protodioscin and the HPDE5 receptor has van der waals bonds, hydrogen bonds, carbon hydrogen bonds, atraktive charge bonds, pi cation bonds, pi–Stacked bonds or T-Shape pi bonds, and alkyl bonds. The interaction between the chemical compound icariin and the HPDE5 receptor has van der waals bonds, carbon hydrogen bonds, hydrogen bonds, pi sigma bonds, stacked pi bonds, and alkyl bonds. The interaction between the chemical compound yohimbine and the HPDE5 receptor has a carbon hydrogen bond, a pi sigma bond, a T-Shape pi bond, and an alkyl bond. The interaction between the chemical compound ginsenoside and the HPDE5 resptor has van der waals bonds, hydrogen bonds, carbon hydrogen bonds, pi anion bonds, and alkyl bonds. The results of molecular docking and amino acid residues of sildenafil, niloticin, stigmasterol, protodioscin, icariin, yohimbine and ginsenoside against HPDE5 receptors will be shown in figure 2.

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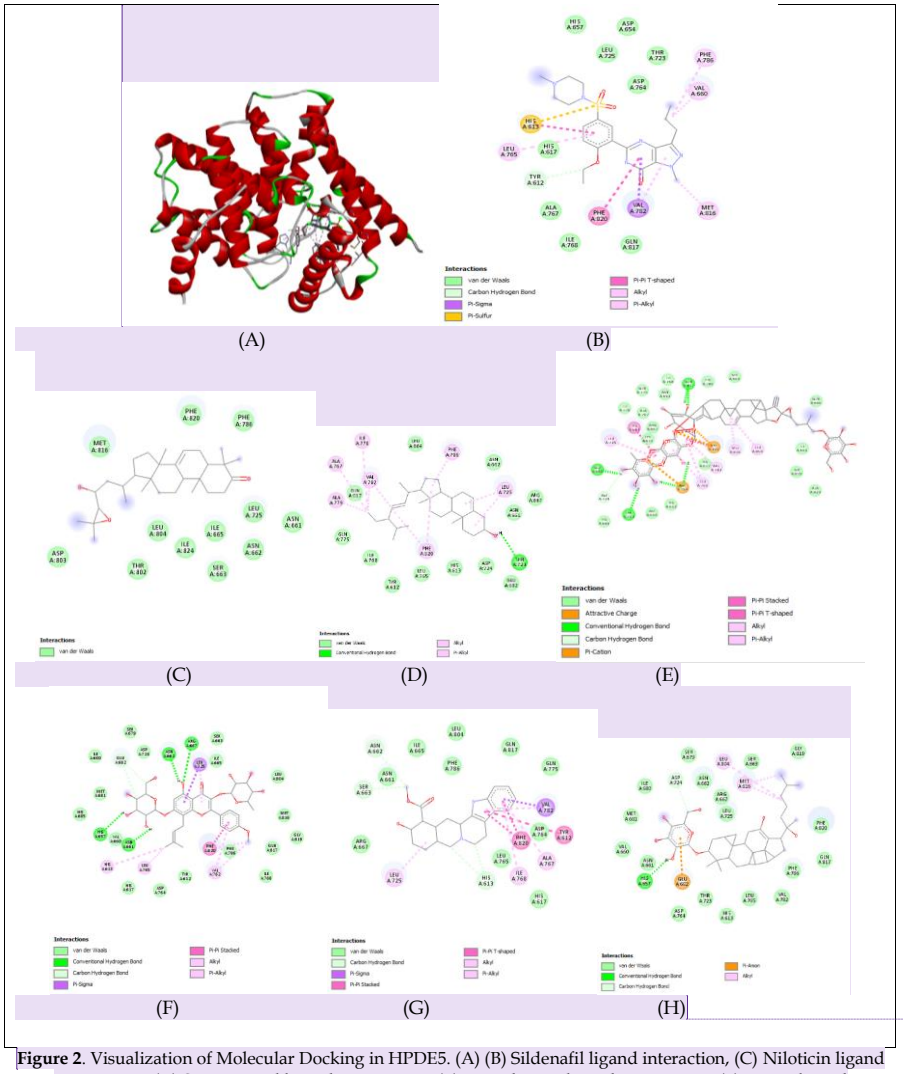

Figure 2. Visualization of Molecular Docking in HPDE5. (A) (B) Sildenafil ligand interaction, (C) Niloticin ligand interactions, (D) Stigmasterol ligand interactions, (E) Protodioscin ligand interactions, (F) Icariin ligand interactions, (G) Yohimbine ligand interactions, (H) Ginsenoside ligand interactions

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Table 2. Lipinski's Rule of Five Test Results

No	Ligan	Interaction						
		Van der Waals	Hidrogen	Hidrogen karbon	Sigma	Sulfur Anion Cation	T-Shape	Alkil
1	Sildenafil -9,5 kkal/mol			TYR 612	**VAL 782**	HIS 613	**PHE 820**	**PHE 786**, VAL 660, **MET 816,** LEU 765
2	Niloticin -7,8 kkal/mol							
3	Stigmasterol -10,7 kkal/mol		THR 723					ALA 767, ALA 779, VAL 782, ILE 778, PHE 820, **PHE 786,** LEU 725
4	Protodioscin -13,1 kkal/mol	ASP 724	GLN 817, THR 723	ASP 724		ASP 764, PHE 820	HIS 613	LEU 725, LEU 764, LEU 804, VAL 765, **MET 816**
5	Icariin -11,1 kkal/mol	GLU 682	HIS 657, ASN 661, ASN 662, ARG 667	GLU 682	LEU 725		**PHE 820**	HIS 613, **LEU 765,** VAL 782
6	Yohimbine -10,1 kkal/mol			ASN 662, SER 663, HIS 613,	**VAL 782**		TYR 612 **PHE 820**	ALA 767, ILE 768, LEU 725
7	Ginsenosid -12,1 kkal/mol	ASP 724	HIS 657	ASP 724		GLU 612		LEU 807, **MET 816**

Based on table 1, the test ligand compounds namely ginsenoside, yohimbine, protodioscin, icariin, and stigmasterol have a higher bond energy compared to sildenafil. From the results of bond energy, sildenafil has a bond energy value of -9.5 kcal / mol, protodioscin compounds -13.1 kcal/mol, ginsenoside -12.1 kcal / mol, icariin -11.1 kcal / mol, stigmasterol -10.7 kcal / mol, and yohimbine -10.1 kcal / mol.

Bond energy describes the strength of bond affinity resulting from the interaction of ligands and receptors. The binding energy of the scoring results is in the form of Gibbs free energy (ΔG). If ΔG < 0 the reaction runs spontaneously (the reaction goes to the product). ΔG = 0 reversible running reactions. If ΔG > 0 the reaction does not occur (the reaction goes in the direction of the reactant). The smaller the ΔG value, the stronger the bond that occurs between the ligand and the receptor, the more stable it is. The compounds niloticin, icariin, stigmasterol, protodioscin, ginsenoside, yohimbine, and sildenafil are negative which means that the reaction can occur and run spontaneously (the reaction goes towards the product) so that the bond between the test ligands of the compounds niloticin, icariin, stigmasterol, protodioscin, ginsenoside, yohimbine, and sildenafil with the Human Phosphodiesterase 5 receptor becomes stable.

The interaction that occurs between ligands and proteins is not only in the form of hydrogen bonds, but

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also other non-covalent interactions that can increase the inhibitor's affinity for receptors. Hydrogen bonds can affect the chemical-physical properties of compounds, such as boiling point, melting point, solubility in water, ability in chelate formation and acidity. Changes in these properties can affect the biological activity of the compound. Van der waals bonds produce electrostatic interactions that are interactions between atoms due to differences in their polarity. This interaction belongs to weak and non-covalent interactions so that it is easy to release, but due to its large number of electrostatic interactions have a great contribution in the formation of protein conformation. Hydrophobic interactions are also formed through pi-sigma and alkyl bonds as well as carbon hydrogen bonds.

Based on the results of molecular molecular docking analysis between protodioscin, ginsenoside, icariin, stigmasterol and yohimbine compounds against PDE5 receptors, it shows that the test ligand compounds have a greater bond energy than comparison ligands (sildenafil) and there are the same amino acid bonds and residues between sildenafil and the test compound. The similarity of activity is characterized by the similarity of the results of amino acid residues and the bonding of the test ligand molecular docking results with the original ligands.

Test Lipinski's Rule of Five

Lipinski's Rule of Five is a softwere that can be used to determine the physicochemical properties of ligands to determine the hydrophobic/hydrophilic character of a compound through cell membranes by passive diffusion (Jasmine, 2021). The results of Lipinski's Rule of Five test are shown in table 2.

Table 2. Lipinski's Rule of Five Test Results

Compound	Mass	Donor H	Acceptor H	Log P	MR	Information
Sildenafil	474	1	5	2,6	124	Eligible
Ginsenoside	312	5	6	-0,05	77	Eligible
Icariin	676	8	15	-0,12	163	Ineligible
Niloticin	456	1	3	6,7	132	Ineligible
Protodioscin	312	5	6	-0,05	77	Eligible
Stigmasterol	412	1	1	7,8	128	Ineligible
Yohimbine	354	2	4	2,6	98	Eligible
Syarat	<500	<5	<10	<5	40-130	

Based on the table 2, it can be seen that there are 3 test ligand compounds that meet the requirements of Lipinski's Rule of Five, these compounds include ginsenoside, protodioscin, and yohimbine. However, in the compounds icariin, niloticin, and stigmasterol do not qualify lipinski rules.

Ligands with a molecular weight of < 500 Da more easily penetrate the cell membrane compared to ligands whose molecular weight > 500 Da. Molecular weights that are too large will reduce the effectiveness of biology so that if the compound is too large it will take a long time to be absorbed by the body(Alfathin, Herawati, & Faqih, 2009).

Log P values are related to the lipofility or hydrophobility of drug molecules, namely the ability of a chemical compound to dissolve in fat, oil or non-polar solvents. A Log P value greater than 5 signifies a more hydrophobic and fat-soluble compound. In other words, the molecule can easily penetrate the membrane barrier so that it will cause the drug compound to tend to have a high level of toxicity. Log P values that are too negative are also not good because the molecule cannot pass through the lipid bilayer membrane (Adriani, 2018).

The number of hydrogen donors and acceptors describes that the higher the hydrogen bond capacity, the higher the energy required for the absorption process to occur. In general, Lipinski's Rule of Five describes the solubility of certain compounds to penetrate cell membranes by passive diffusion. Molar Refractivity (MR) is a measure of the total polarisability value of a drug molecule. A good parameter value according to Lipinski's rule is 40-130. The greater the value of Molar Refractivity, the better the permeability of the compound (Alfathin et al., 2009).

Conclusion

The active compounds niloticin, stigmasterol, protodioscin, icariin, yohimbine, and ginsenoside can be molecular docking to the HPDE5 receptor with bond energy values of -7.8 kcal/mol for niloticin, -10.7

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kcal/mol for stigmasterol, -13.1 kcal/mol for protodioscin, -11.1 kcal/mol for icariin, -10.1 kcal/mol for yohimbine and -12.1 kcal/mol for ginsenoside. The interaction that occurs between the active compounds stigmasterol, protodioscin, icariin, yohimbine, and ginsenoside against the HPDE5 receptor forms the same type of bond with sildenafil namely carbon hydrogen, sigma, sulfur cation anion, T-shape and alkyl with some similarities of amino acid residues in each type of bond. From these results it can be suspected that all test compounds have activity as aphrodisiacs except nilocitin compounds.

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Effectiveness of Active Compounds of Herbal Plants as Aphrodisiacs Through Molecular Docking Against Human Phosphodiesterase-5 Receptors

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Abstract: Based on the evaluation of side effects the use of sildenafil as a human phosphodiesterase 5 inhibitor drug (HPDE5) has prompted the search for new compounds that have the potential to be aphrodisiacs. The purpose of this study was to determine the interaction of the active compounds nilocitin, stigmasterol, protodioscin, icariin, yohimbine, and ginsenoside against the HPDE5 receptor as an aphrodisiac. The method used in this study was experimental conducted in silico. The metabolite structure is downloaded from the PubChem application, the protein is downloaded from PDB (Protein Data Bank) with the code 2H42. The result of this study is that the active compound may interact with HPDE5 receptors. The interaction that occurs results in the formation of van der waals bonds, hydrogen, carbon hydrogen, sigma, sulfur cation anions, T-shape and alkyls. The active compounds each have a sildenafil bond energy of -9.5 kcal/mol; niloticin -7.8 kcal/mol; stigmasterol -10.7 kcal/mol; protodioscin -13.1 kcal/mol; icariin -11.1 kcal/mol; yohimbine -10.1 kcal/mol and ginsenoside -12.1 kcal/mol with RMSD 0. The interaction with the HPDE5 receptor results in the formation of the same amino acid residue as the comparison ligand. The residual equation shows that the compounds have the same activity and can be predicted as aphrodisiacs.

Keywords: Aphrodisiac herbs; Erectile dysfunction; Human phosphodiesterase 5; In silico

Introduction

Sexual dysfunction is the inability to achieve satisfactory sexual intercourse in the form of erectile dysfunction (ED), reduced libido, and abnormal ejaculation (Sin et al., 2020). DE is the sexual dysfunction disorder with the highest prevalence, this state can affect emotional and physical self-esteem, psychosocial conditions such as depression, anxiety, and quality of life disorders (Kazemi et al., 2021) and a significant impact on the quality of life of sufferers (Winarta et al., 2020). The prevalence of ED in men aged 40-75 years was 52%, and mild, moderate, and complete DE was 2.17%, 2.25%, and 6.9%, respectively (Maleki-Saghooni et al., 2020). Age is one of the factors that can influence the occurrence of DE, where ED increases with age (Goldstein et al., 2020).

DE that cannot be cured with lifestyle changes, requires support with therapies such as Human Phosphodiesterase 5 inhibitors (HPDE5) (Raheem et al., 2021). HPDE5 inhibitors are the second-line treatment for ED after behavior modification, since this drug is of the nature of only helping to improve the quality of

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erections for men by increasing blood flow in the corpora cavernosa (Ganapathy et al., 2020).

PDE5 is one of the enzymes that plays a key role in regulating many GMP-mediated physiological processes, so HPDE5 inhibitors are the target of various health disorders such as erectile dysfunction, pulmonary and cardiovascular hypertension (Ahmed et al., 2021) (Isidori et al., 2021). Based on the evaluation of side effects occurring from the use of synthetic drug inhibitors HPDE5 has prompted the search for new compounds that have the potential to be aphrodisiacs. Natural aphrodisiac active compounds usually come from the flavonoid group, alkaloids, and also steroid saponins (Gunawan, 2020; Wang et al., 2022).

Some active compounds that are thought to have aphrodisiac activity are niloticin from the Eurycoma longifolia plant (*Eurycoma longifolia Jack*.) (Hadi et al., 2020), stigmasterol from purwoceng plant (*Pimpinella alpina Molk*) (Abdullah et al., 2021), protodioscin from rujak polo plant (*Tribulus terrestris*) (Maleki-Saghooni et al., 2020), Icariin from goat horn grass plants (*Epimedium sp*.) (Ganapathy et al., 2021), Yohimbine from yohimbe (*Pausinystalia johimbe*) plant (Brunetti et al., 2020) and ginsenoside from chinese ginseng plant (*Panax ginseng Mayer*) (Lin et al., 2022).

Along with the times, the discovery or development of new drugs is now easier to do so that in new drug planning begins to limit the treatment of test animals because it takes time and costs a lot and a code of ethics is needed for the use of test animals. Therefore, in silico began to be looked at because of its cheap advantages and faster results. In silico is a research method that utilizes computing technology and databases to develop further research (Makatita et al., 2020). The in-silico method is a computer-based research study. The use of the in silico method has been used to predict the pharmacological effects of compounds on the target genes studied (Bare et al., 2019) and played a role in the design and discovery of bioactive compounds in the drug development process (Kesuma et al., 2018).

In this study, molecular docking will be carried out using the in silico method, ligand and protein structures downloaded from the Protein Data Bank database and then molecular tethering is carried out using PyRx software and BIOVIA Discovery Studio to determine the interaction and affinity of the bond energy so that the chemical content of the active ingredient in the plant can be used as the basis for drug discovery that is predicted to have the strongest potential as a natural aphrodisiac candidate.

Method

This research is a type of experimental research using the in-silico method. This research will carry out the molecular docking process of the compounds niloticin, stigmasterol, protodioscin, icariin, yohimbine and ginsenoside against the HPDE5 receptor to determine its interaction as an aphrodisiac. The tests carried out are ligand and receptor preparation, ligand and receptor preparation, validation, molecular molecular docking using Pyrx-Autodock Vina and visualization with BIOVIA Discovery Studio Visualizer.

Tool

The tools used in this study are hardware in the form of an Asus-X441M Laptop with an Intel® inside™ N-4000 CPU @2.6 GHz processor, 4.00 GB of RAM. The software used is Pyrx-Autodock and Vina, and BIOVIA Discovery Studio.

Material

The ingredients used in in silico research are the structure of natural compounds that have the potential to be aphrodisiacs, namely niloticin, stigmasterol, protodioscin, icariin, yohimbine and ginsenoside and the chemical compound sildenafil (PDE5 inhibitor) downloaded in the Pubchem application database (https://pubchem.ncbi.nlm.nih.gov/). HPDE5 receptors downloaded in the Protein Data Bank (https://www.rcsb.org/).

Research Procedure: Ligan Preparation

The ligands to be used are niloticin compounds, stigmasterol, protodioscin, icariin, yohimbine and ginsenoside and sildenafil chemical compounds downloaded in the Pubchem database in the form of 3D conformation with SDF format.

Research Procedure: Preparasi Reseptor

Receptor preparation is carried out by downloading PDE5 in the Protein Data Bank with PDB format. The protein is cleaned from water molecules so as not to interfere at the time of docking simulation. If the receptors are clean then polar hydrogen is added to the chemistry>>hydrogen>>add>>polar only>>ok options. The ligand and receptor structure is then opened with the application of Pyrx- AutoDock first to prepare the ligands and receptors, the stages are as follows: added ligands and receptors of PDB format in the applicationPyrx- AutoDock then select the ligand file and convert to pdbqt. Furthermore, the receptors and receptors will be displayed in PDBQT format.

Research Procedure: Validation

The molecular docking validation process is carried out using the Pyrx-vina application by preparing a place where ligands will inhibit the receptor by arranging the gridbox on the active side of

the receptor or by covering the entire molecule. Adjust the gridbox at the specified coordinates (center x, y, z).

Molecular docking of niloticin, stigmasterol, protodioscin, icariin, yohimbine and ginsenoside compounds in human phosphodiesterase 5

The Pyrx application is run using vinawizard and waited until the running process is complete. After the molecular docking is completed, the binding results of the ligands studied will appear. Save the dataexcel containing the energy value of its bond and save the result of docking between the ligandand receptors in PDB format.

Visualization of the Structure

The last stage in the molecular docking process is visualization. The docking results with the best conformation were then analyzed using Discovery Studio and then viewed the results in 2D and 3D form.

Test Lipinski's Rule of Five

The steps to test plant chemical compounds, first open the website http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp then the chemical structure of the compound in 3D form in the form of PDB is inputted at the normal pH value (7) and finally click submit.

Result and Discussion

Ligan Preparation

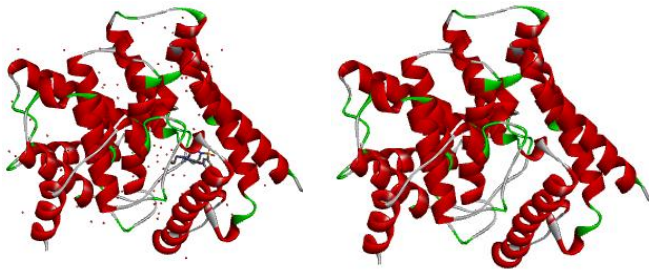
The initial stage of the study is to conduct a search for ligands. The ligands tested in this study are compounds that are predicted to have activity as an aphrodisiac (Atanda et al., 2022). These compounds include niloticin, stigmasterol, protodioscin, icariin, yohimbine and ginsenoside. The ligands to be tested are obtained or downloaded in 3D conformation form in SDF format from the PubChem database. The prepared ligands are prepared, namely by changing the ligand format of the SDF into the form of a Protein Data Bank (PDB) so that molecular molecular docking can be carried out.

Sildenafil is the first active ingredient used as a peroral DE disorder therapy, working through inhibition of Phosphodiesterase 5 (PDE5) approved by the Food and Drug Administration (FDA) for the treatment of DE (Ongaro et al., 2021). In this study, sildenafil functioned as a comparison ligand. Sildenafil is downloaded from the PubChem database in the form of a 3D conformer with SDF format which is then prepared ligands by converting the format into the form of a Protein Data Bank (PDB).

Luteinizing Hormone is a glycoprotein hormone associated with follicle-stimulating and thyroid-stimulating hormone. Luteinizing hormone is very important in human reproduction and is a hormone that plays an important role in being used as the basis for drug discovery for endocrine diseases (Duan et al., 2021). Luteinizing hormone in this study was used as a native ligand or natural ligand from the body downloaded from the Protein Data Bank (PDB) with the code 7FIJ. This hormone is in the form of proteins or macromolecules so that molecular docking cannot be done against the HPDE5 receptor because the pyrx application is not compatible with docking between proteins.

Receptor Preparation

The macromolecule that will be used in the molecular docking process is Human Phosphodiesterase 5 (HPDE5). Optimization is carried out by removing solvent molecules or solvents, namely water. This is so as not to interfere with the molecular molecular docking process. After the removal of water molecules, the addition of hydrogen atoms is necessary because the presence of hydrogen atoms can affect the results of molecular interactions. After ligand separation and optimization, the results of PDE5 macromolecules are stored in the form of PDB files. The results of receptor preparation are shown in figure 1.



(a) (b)

Figure 1. HPDE5 Receptor Preparation Results, (A) before preparation, (B) after preparation Validasi.

Validation is carried out in the absence of water because it will block ligand bonds with its receptors because water can form hydrogen bonds with receptors (Ruswanto et al., 2018). Validation of molecular docking is done with the gridbox settings. Gridboxes are the sides of the area to be shot, where the smaller the gridbox, the hope is that the more precise it will be and the results obtained will be more accurate. The gridbox is set on the active side of the receptor or by covering the entire part of the molecule so that the ligand can place where it will inhibit the receptor. The gridbox is adjusted at center coordinates x = 22.4305; y = 126.2819; and z = 13.9905 and at dimensions x = 62.6329, y = 58.9924, and z = 61.1605 Angstrom. Then molecular docking is carried out using Pyrx-Autodock

Vina so that a Root Mean Square Deviation is produced. RMSD indicates the distance of atoms in a conformation, the smaller the RMSD value, the better the ligand position because it is close to the conformation of the ligand origin. The value of RMSD depends on the interaction of bonds and energy between proteins and ligands, the smaller the RMSD value, the more similar the structure of the reacted ligand. The rmsd value received is less than two.

Molecular docking

In this study, testing niloticin, stigmasterol, protodioscin, icariin, yohimbine and ginsenoside compounds as well as PDE5 Inhibitors (sildenafil) was carried out by molecular docking these compounds with HPDE5 receptors. The file format of the active compound will be changed automatically in the open babel program, then by doing the same gridbox settings with molecular docking validation, the molecular docking process of the entire test ligand is carried out. The result of molecular docking is the value of RMSD and gibbs free energy (ΔG), as well as ligand conformation with the file format, pdbqt.

Visualization of sildenafil, niloticin, stigmasterol, protodioscin, icariin, yohimbine and ginsenoside against HPDE5 receptors

The interaction between the chemical compound sildenafil and the HPDE5 receptor has carbon hydrogen bond, sigma pi bond, sulfur pi bond, T-Shape pi bond, and alkyl bond. The interaction between the chemical compound niloticin and the HPDE5 receptor no bonds formed. The interaction between the chemical compound stigmasterol and the HPDE5 receptor has a hydrogen bond and alkyl bond. The interaction between the chemical compound protodioscin and the HPDE5 receptor has van der waals bonds, hydrogen bonds, carbon hydrogen bonds, atraktive charge bonds, pi cation bonds, pi–Stacked bonds or T-Shape pi bonds, and alkyl bonds. The interaction between the chemical compound icariin and the HPDE5 receptor has van der waals bonds, carbon hydrogen bonds, hydrogen bonds, pi sigma bonds, stacked pi bonds, and alkyl bonds. The interaction between the chemical compound yohimbine and the HPDE5 receptor has a carbon hydrogen bond, a pi sigma bond, a T-Shape pi bond, and an alkyl bond. The interaction between the chemical compound ginsenoside and the HPDE5 resptor has van der waals bonds, hydrogen bonds, carbon hydrogen bonds, pi anion bonds, and alkyl bonds. The results of molecular docking and amino acid residues of sildenafil, niloticin, stigmasterol, protodioscin, icariin, yohimbine and ginsenoside against HPDE5 receptors will be shown in figure 2.

Based on table 1, the test ligand compounds namely ginsenoside, yohimbine, protodioscin, icariin, and stigmasterol have a higher bond energy compared to sildenafil. From the results of bond energy, sildenafil has a bond energy value of -9.5 kcal / mol, protodioscin compounds -13.1 kcal/mol, ginsenoside -12.1 kcal / mol, icariin -11.1 kcal / mol, stigmasterol -10.7 kcal / mol, and yohimbine -10.1 kcal / mol. The compound that has the highest bond energy value is protodioscin, and the compound that has bond energy is niloticin which has a bond energy of -7.8 kcal/mol.

Bond energy describes the strength of bond affinity resulting from the interaction of ligands and receptors. The binding energy of the scoring results is in the form of Gibbs free energy (ΔG). If $\Delta G < 0$ the reaction runs spontaneously (the reaction goes to the product). $\Delta G = 0$ reversible running reactions. If $\Delta G > 0$ the reaction does not occur (the reaction goes in the direction of the reactant). The smaller the ΔG value, the stronger the bond that occurs between the ligand and the receptor, the more stable it is. The compounds niloticin, icariin, stigmasterol, protodioscin, ginsenoside, yohimbine, and sildenafil are negative which means that the reaction can occur and run spontaneously (the reaction goes towards the product) so that the bond between the test ligands of the compounds niloticin, icariin, stigmasterol, protodioscin, ginsenoside, yohimbine, and sildenafil with the Human Phosphodiesterase 5 receptor becomes stable.

The interaction that occurs between ligands and proteins is not only in the form of hydrogen bonds, but also other non-covalent interactions that can increase the inhibitor's affinity for receptors. Hydrogen bonds can affect the chemical-physical properties of compounds, such as boiling point, melting point, solubility in water, ability in chelate formation and acidity. Changes in these properties can affect the biological activity of the compound. Van der waals bonds produce electrostatic interactions that are interactions between atoms due to differences in their polarity. This interaction belongs to weak and non-covalent interactions so that it is easy to release, but due to its large number of electrostatic interactions have a great contribution in the formation of protein conformation. Hydrophobic interactions are also formed through pi-sigma and alkyl bonds as well as carbon hydrogen bonds.

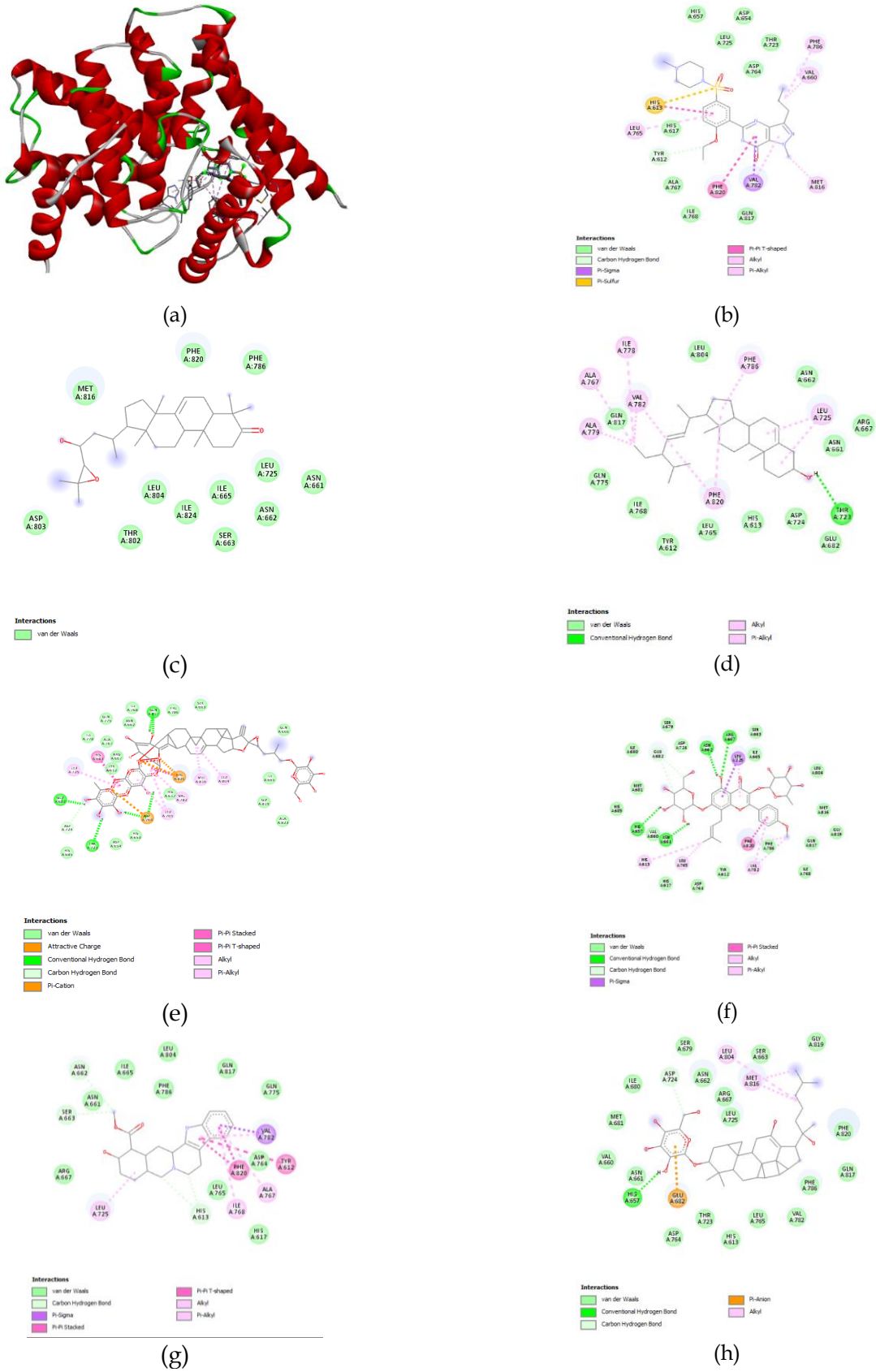


Figure 2. Visualization of Molecular Docking in HPDE5. (A) (B) Sildenafil ligand interaction, (C) Niloticin ligand interactions, (D) Stigmasterol ligand interactions, (E) Protodioscin ligand interactions, (F) Icariin ligand interactions, (G) Yohimbine ligand interactions, (H) Ginsenoside ligand interactions

Table 1. Lipinski's Rule of Five Test Results

Ligan	Interaction						
	Van der Waals	Hidrogen	Hidrogen karbon	Sigma	Sulfur Anion Cation	T-Shape	Alkil
Sildenafil -9,5 kkal/mol			TYR 612	VAL 782	HIS 613	PHE 820	PHE 786, VAL 660, MET 816, LEU 765
Niloticin -7,8 kkal/mol							
Stigmasterol -10,7 kkal/mol		THR 723					ALA 767, ALA 779, VAL 782, ILE 778, PHE 820, PHE 786, LEU 725
Protodioscin -13,1 kkal/mol	ASP 724	GLN 817, THR 723	ASP 724		ASP 764, PHE 820	HIS 613	LEU 725, LEU 764, LEU 804, VAL 765, MET 816
Icariin -11,1 kkal/mol	GLU 682	HIS 657, ASN 661, ASN 662, ARG 667	GLU 682	LEU 725		PHE 820	HIS 613, LEU 765, VAL 782
Yohimbine -10,1 kkal/mol			ASN 662, SER 663, HIS 613,	VAL 782		TYR 612 PHE 820	ALA 767, ILE 768, LEU 725
Ginsenosid -12,1 kkal/mol	ASP 724	HIS 657	ASP 724		GLU 612		LEU 807, MET 816

Based on the results of molecular molecular docking analysis between protodioscin, ginsenoside, icariin, stigmasterol and yohimbine compounds against PDE5 receptors, it shows that the test ligand compounds have a greater bond energy than comparison ligands (sildenafil) and there are the same amino acid bonds and residues between sildenafil and the test compound. The similarity of activity is characterized by the similarity of the results of amino acid residues and the bonding of the test ligand molecular docking results with the original ligands.

Test Lipinski's Rule of Five

Lipinski's Rule of Five is a softwere that can be used to determine the physicochemical properties of ligands to determine the hydrophobic/hydrophilic character of a compound through cell membranes by passive diffusion (Jasmine, 2021). The results of Lipinski's Rule of Five test are shown in table 2.

Table 2. Lipinski's Rule of Five Test Results

Compound	Mass	Donor H	Acceptor H	Log P	MR	Information
Sildenafil	474	1	5	2,6	124	Eligible
Ginsenoside	312	5	6	-0,05	77	Eligible
Icariin	676	8	15	-0,12	163	Ineligible
Niloticin	456	1	3	6,7	132	Ineligible
Protodioscin	312	5	6	-0,05	77	Eligible
Stigmasterol	412	1	1	7,8	128	Ineligible
Yohimbine	354	2	4	2,6	98	Eligible
Syarat	<500	<5	<10	<5	40-130	

Based on the table 2, it can be seen that there are 3 test ligand compounds that meet the requirements of Lipinski's Rule of Five, these compounds include ginsenoside, protodioscin, and yohimbine. However, in the compounds icariin, niloticin, and stigmasterol do not qualify lipinski rules.

Ligands with a molecular weight of < 500 Da more easily penetrate the cell membrane compared to ligands whose molecular weight > 500 Da. Molecular weights that are too large will reduce the effectiveness of biology so that if the compound is too large it will take a long time to be absorbed by the body (Alfathin et al., 2021).

Log P values are related to the lipofility or hydrophobility of drug molecules, namely the ability of a chemical compound to dissolve in fat, oil or non-polar solvents. A Log P value greater than 5 signifies a more hydrophobic and fat-soluble compound. In other words, the molecule can easily penetrate the membrane barrier so that it will cause the drug compound to tend to have a high level of toxicity. Log P values that are too negative are also not good because the molecule cannot pass through the lipid bilayer membrane (Adriani, 2018).

The number of hydrogen donors and acceptors describes that the higher the hydrogen bond capacity, the higher the energy required for the absorption process to occur. In general, Lipinski's Rule of Five describes the solubility of certain compounds to penetrate cell membranes by passive diffusion. Molar Refractivity (MR) is a measure of the total polarisability value of a drug molecule. A good parameter value according to Lipinski's rule is 40-130. The greater the value of Molar Refractivity, the better the permeability of the compound (Alfathin et al., 2021).

Conclusion

The active compounds niloticin, stigmasterol, protodioscin, icariin, yohimbine, and ginsenoside can be molecular docking to the HPDE5 receptor with bond energy values of -7.8 kcal/mol for niloticin, -10.7 kcal/mol for stigmasterol, -13.1 kcal/mol for protodioscin, -11.1 kcal/mol for icariin, -10.1 kcal/mol for yohimbine and -12.1 kcal/mol for ginsenoside. The interaction that occurs between the active compounds stigmasterol, protodioscin, icariin, yohimbine, and ginsenoside against the HPDE5 receptor forms the same type of bond with sildenafil namely carbon hydrogen, sigma, sulfur cation anion, T-shape and alkyl with some similarities of amino acid residues in each type of bond. From these results it can be suspected that all test compounds have activity as aphrodisiacs except nilocitin compounds.

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