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Identification of Potential PDE5 Inhibitors from Natural Sources for Erectile Dysfunction Therapy Through A Molecular Docking Approach

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ABSTRACT
The global prevalence of erectile dysfunction has increased in recent decades, and despite various treatment modalities, including phosphodiesterase-5 (PDE5) inhibitors, side effects and contraindications necessitate alternative therapies. This research explores the potential of active compounds present in aphrodisiac plants as PDE5 inhibitors using a molecular docking approach. Eight test compounds evaluated, namely quercitrin, quercetin, garcinoic acid, ellagic acid, catechin, and kaempferol, exhibited high affinity towards PDE5. Receptor-ligand analysis revealed interacting residues supporting PDE5 inhibition. Pharmacokinetic analysis demonstrated similarities, particularly in terms of bioavailability and toxicity, among these ligands, except for quercitrin when compared to the control ligand, sildenafil. This study found that compounds derived from herbal sources show potential as PDE5 inhibitors, with pharmacokinetic profiles comparable to sildenafil. Experimental validation is required to verify the efficacy of these ligands.
Key words: *Erectile Dysfunction; Herbal Compounds; In Silico; Molecular Docking; PDE5 Inhibitors*

INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to maintain an erection sufficient for sexual activity (Aytaç et al., 1999). Estimates indicated that the global prevalence of erectile dysfunction reached approximately 322 million cases in 2025, increasing from 152 million in 1995, and establishing it as one of the most prevalent male sexual health disorders worldwide (Aytaç et al., 1999). Research such as the Massachusetts Male Ageing Study (MMAS) and the European Male Ageing Study (EMAS) (Corona et al., 2010) shows a higher incidence in older age groups. In Indonesia, a survey at Cipto Mangunkusumo Hospital by Birowo et al. (2019) recorded a prevalence of ED of 35.6%, with distribution varying from 6.5% in the 20-29 age group to 88.0% in respondents aged 60 and over.

ED is associated with dysfunction in the erection process involving neurological factors, such as adrenergic and myogenic control, as well as enzymatic factors. Enzymatic factors cause ED due to an imbalance of endothelium-derived relaxing factors, primarily nitric oxide (NO), and endothelium-derived contracting factors, namely prostaglandin and endothelin (Hellstrom, 2007). Phosphodiesterase-5 (PDE5) functions to increase intracellular Ca^{2+} levels in the smooth muscle of penile tissue through the hydrolysis of cGMP, thereby inhibiting adequate blood flow to the corpus cavernosum and causing penile flaccidity (Li et al., 2014). Disruption in the production of NO or cGMP leads to dysfunction of penile tissue and ED (Giuliano et al., 2013).

Although various treatment strategies have been developed, including lifestyle modifications and the use of PDE5 inhibitors such as sildenafil (Viagra), their side effects and contraindications carry serious implications (Barnard et al., 2021; Klein & Shindel, 2023; Medina-Polo et al., 2020; Yafi et al., 2016). Plants that are widely found in Indonesia and other parts of the world have been utilized to treat ED, such as chives (*Allium tuberosum*), nutmeg (*Myristica fragrans*), moringa (*Moringa oleifera*), velvet bean (*Mucuna pruriens*), *Garcinia kola*, and pomegranate (*Punica granatum*) (Fauzi et al., 2019). Research shows that their bioactive components, such as flavonoids and saponins, exhibit inhibitory effects on enzymes related to ED, particularly PDE5

(Duangnin et al., 2017; Goswami et al., 2014; Guohua et al., 2009; Odubanjo et al., 2018).

This study aims to determine the potential of the active substances contained in these plants as PDE5 inhibitors by assessing the affinity and interaction of the active substances as ligands when bound to the catalytic domain of PDE5 using molecular docking techniques.

METHOD

The research conducted is an experimental in silico study using molecular docking techniques to investigate the interaction between the catalytic domain of PDE5 and various bioactive compounds. The study was conducted using a laptop with specific hardware and software, along with molecular structures obtained from the Protein Data Bank and test compounds derived from the sample plants, namely catechin, garcinal, and garcinoic acid from *G. kola*; steroid saponins and alkaloids from chives (*A. tuberosum*); ellagic acid, quercitrin, quercetin, and kaempferol from nutmeg (*M. fragrans*) and moringa (*M. oleifera*); 2,4-bis(1,1-dimethylethyl)-phenol from velvet bean (*M. pruriens*); as well as punicalagin and puninic acid from pomegranate (*P. granatum*).

In the preparation stage, the catalytic domain of the PDE5 enzyme, obtained from the Protein Data Bank, was prepared using AutoDock Tools. This process involved the isolation of enzymes from water molecules and non-standard residues. Further preparation involved the addition of hydrogen atoms to the receptor, adjusting its charge to approximate cytoplasmic pH, and correcting the charge by adding Gasteiger charge. Next, a grid box representing the binding area was set up based on specific coordinates, considering the position of amino acids when interacting with ligands (Brandsdal et al., 2003).

Ligands were obtained from PubChem in 3D structure, converted to a format compatible with AutoDock through PyMOL, and optimized for geometry and energy minimization. Identification of the active site of PDE5 involved a dual approach using the web servers CASTp and PrankWeb. Ligand binding to the PDE5 receptor is performed using AutoDock Vina. The results of the binding were analyzed by comparing the main parameters, namely free binding energy (ΔG) among test ligands, which reflect the strength and spontaneity of binding between each ligand and the receptor (Stanzione et al., 2021). Visualization and comparison of interactions, including hydrogen bonds and hydrophobic interactions, were analyzed using Discovery Studio Visualizer to investigate the molecular mechanisms underlying the inhibition process of PDE5 between ligands and the test receptor.

Pharmacokinetic and physicochemical analyses using the SMILES code of each test ligand and control ligand were conducted using the SwissADME web server and pkCSM pharmacokinetics. Analysis of the boiled egg model was also performed to predict passive gastrointestinal absorption and blood-brain barrier (BBB) penetration of bioactive molecules that are useful in the drug design and development process.

RESULTS

In this study, 12 test ligands were selected for molecular docking with sildenafil, the most common PDE5 inhibitor, as the control ligand. Of the 12 selected ligands, only 8 ligands could be processed for molecular docking. The 3D structures of steroid saponins and alkaloids from *A. tuberosum* as well as punicalagin from *P. granatum* could not be downloaded from the PubChem site, while 2,4-bis(1,1-dimethylethyl)phenol from *M. pruriens* could not be processed in AutoDock Tools because its configuration has a silicon (Si) atom that is uncharged.

Furthermore, molecular docking of the test ligands and control ligand (sildenafil) with PDE5 was performed using AutoDock Vina. The results of the docking are presented in **Table 1**. Six molecules showed higher binding affinity with PDE5 compared to sildenafil. Quercitrin, quercetrin, and garcinoic acid had the best binding affinity, reflected by the highest free binding energy (ΔG) value among other test ligands, which is -8.8 kcal/mol, while puninic acid had the lowest value (-5.9 kcal/mol). In comparison, the free binding energy value from the docking results with sildenafil was -8.2 kcal/mol.

Table 1. Results of binding affinity value calculations with AutoDock Vina

Number	Ligand	Binding affinity (ΔG) (kcal/mol)
1.	Quercitrin	-8.8
2.	Quercetin	-8.8
3.	Garcinoic Acid	-8.8
4.	Ellagic Acid	-8.5
5.	Catechin	-8.3
6.	Kaempferol	-8.2
7.	Sildenafil	-8.2
8.	Garcinal	-8.1
9.	Puninic Acid	-5.9

Figures 2-10 provides a visualization of the bonds formed and the key amino acid residues involved in the binding between each test ligand and PDE5 using Discovery Studio Visualizer. Based on the visualization, the test ligands and the control ligand appear to interact significantly at the active site of the PDE5 enzyme receptor, as reflected by the interactions with the amino acid residues. The types of interactions identified include hydrogen bonds, hydrophobic interactions, electrostatic interactions, and Pi interactions.

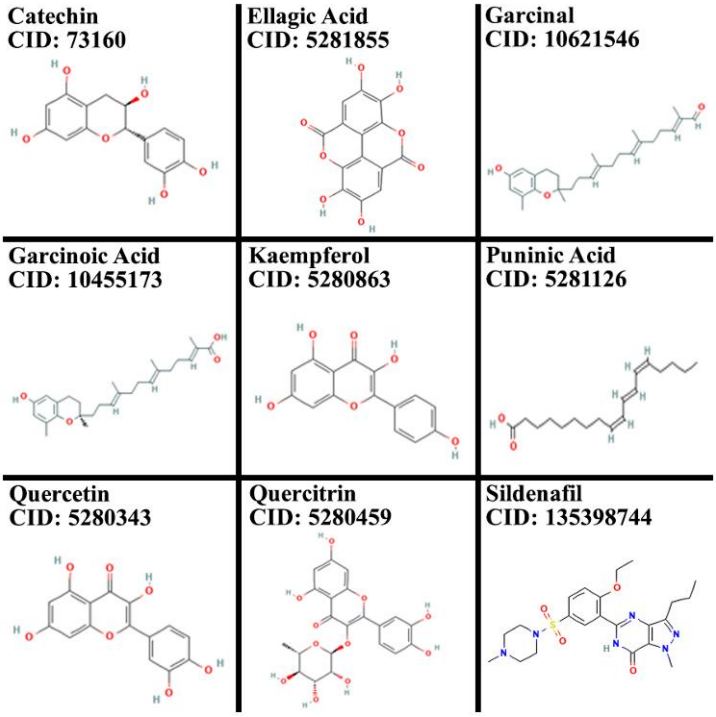

Figure 1. 2D structure and Pubchem compound ID (CID) of test compounds and the control compound (sildenafil)

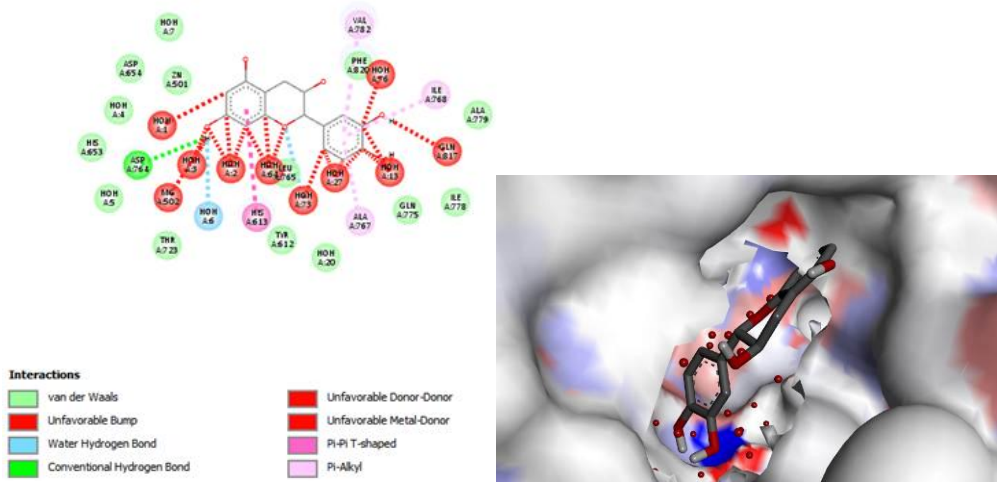

Figure 2. Visualization of the binding results of the PDE5 receptor with catechin in 2D (left) and 3D (right)

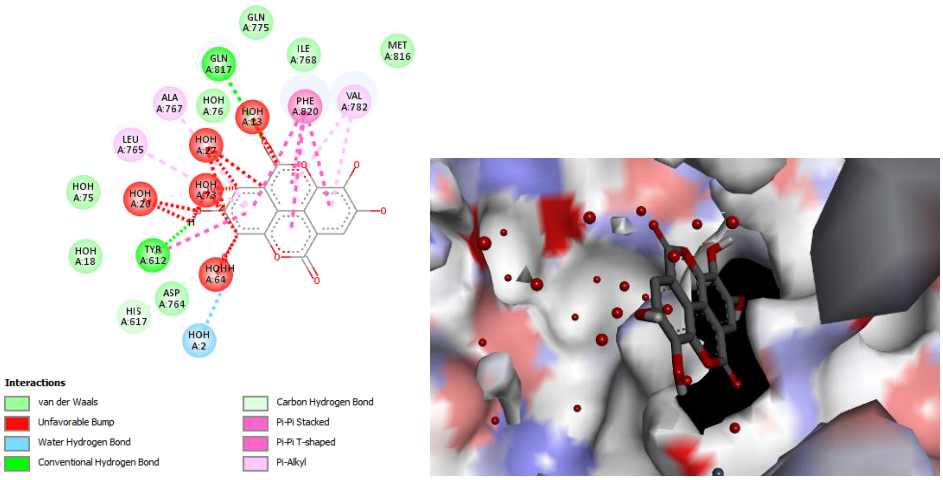

Figure 3. Visualization of the binding results of the PDE5 receptor with ellagic acid in 2D (left) and 3D (right)

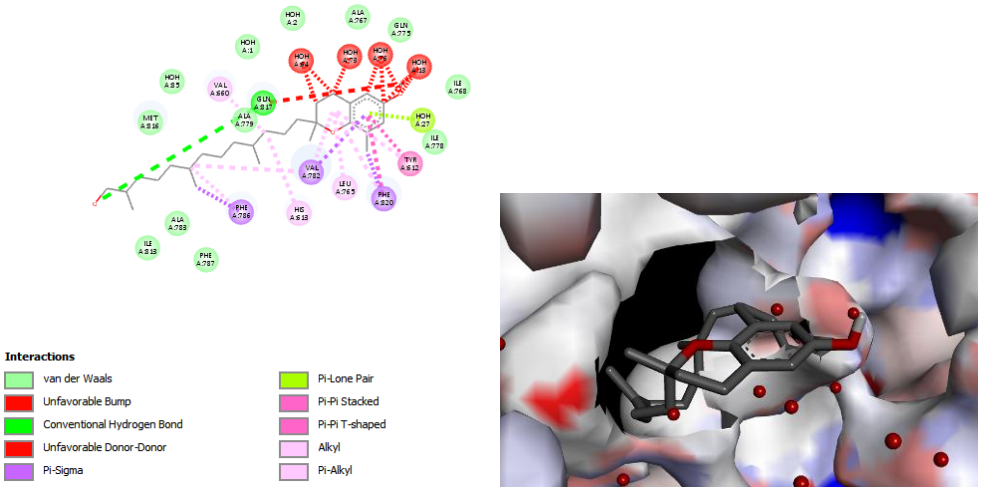

Figure 4. Visualization of the binding results of the PDE5 receptor with garcinal in 2D (left) and 3D (right)

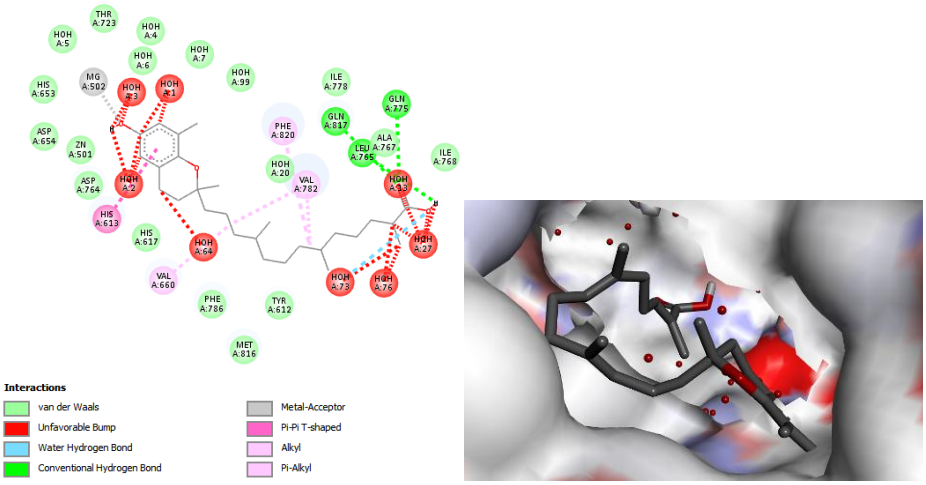

Figure 5. Visualization of the binding results of the PDE5 receptor with garcinoic acid in 2D (left) and 3D (right)

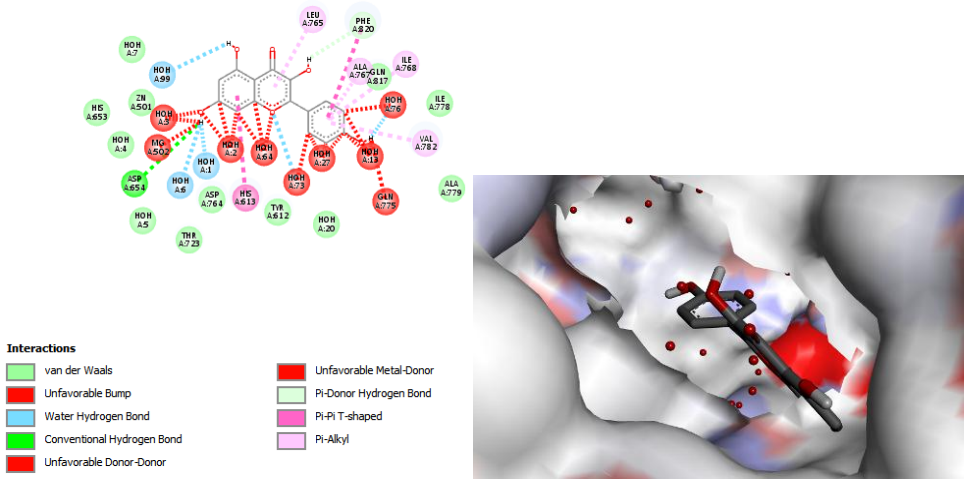

Figure 6. Visualization of the binding results of the PDE5 receptor with kaempferol in 2D (left) and 3D (right)

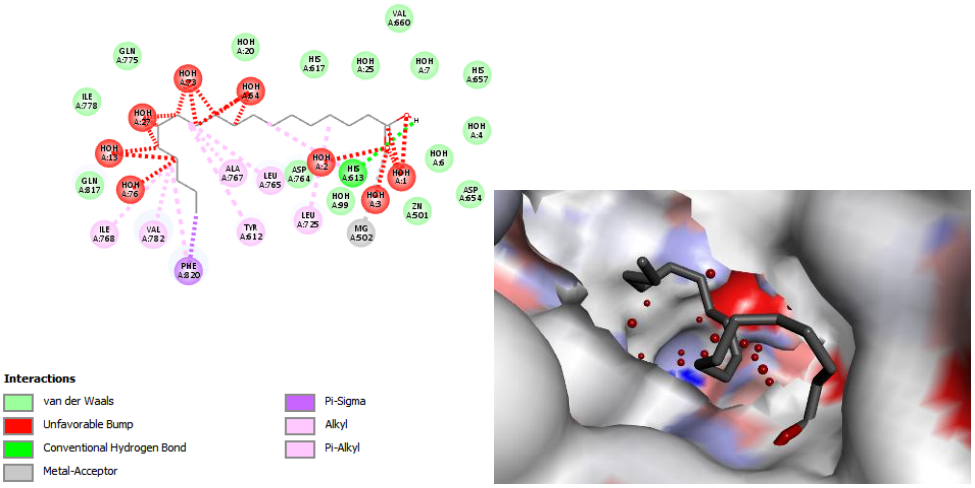

Figure 7. Visualization of the binding results of the PDE5 receptor with puninic acid in 2D (left) and 3D (right)

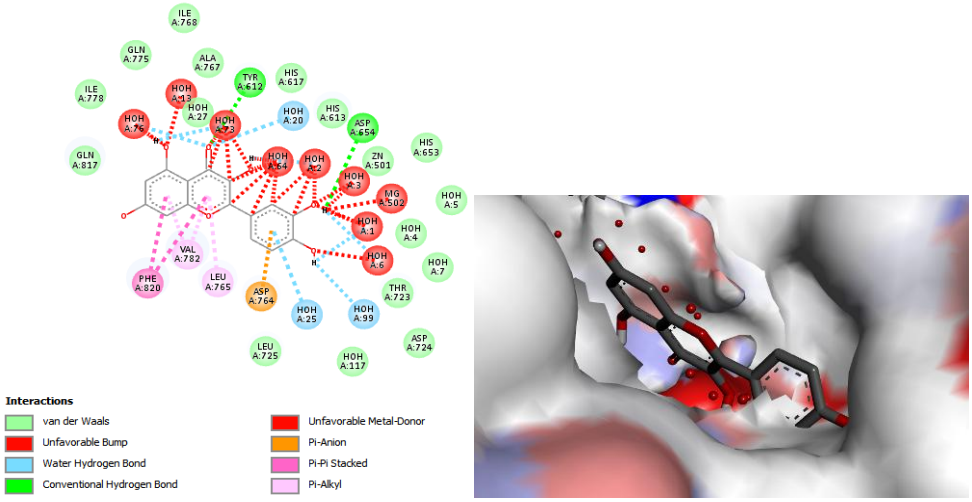

Figure 8. Visualization of the binding results of the PDE5 receptor with quercetin in 2D (left) and 3D (right)

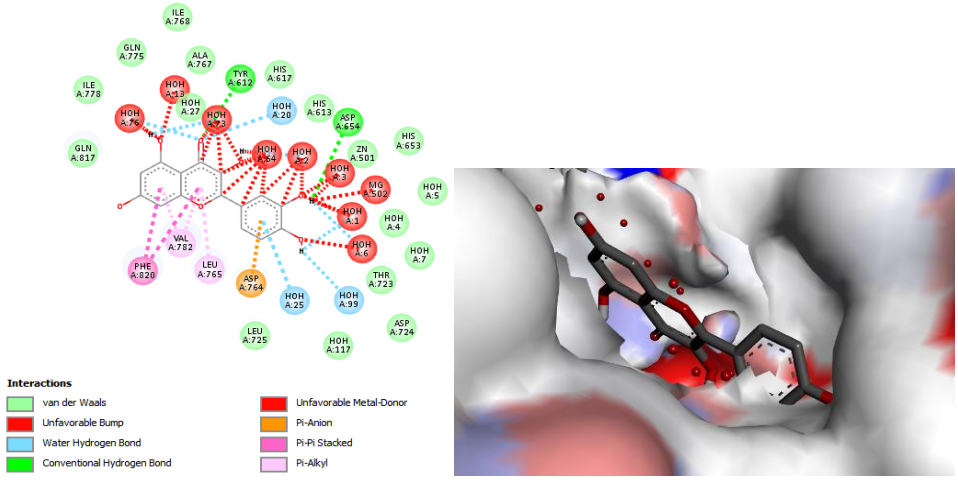

Figure 9. Visualization of the binding results of the PDE5 receptor with quercitrin in 2D (left) and 3D (right)

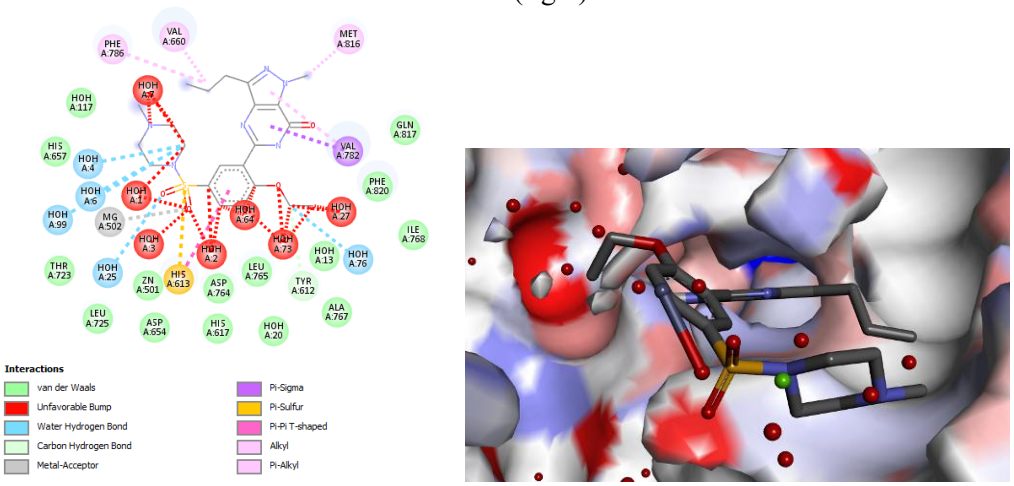

Figure 10. Visualization of the binding results of the PDE5 receptor with sildenafil in 2D (left) and 3D (right)

Pharmacokinetic and physicochemical analyses using the SMILES code of each test ligand and control ligand were conducted using the SwissADME web server and pkCSM pharmacokinetics. The results of the pharmacokinetic and physicochemical analyses are presented in **Table 2**. The results obtained show that all tested ligands had the same bioavailability score when compared to the standard drug (sildenafil). From the aspect of synthetic accessibility, only one ligand, quercitrin, had a score higher than 5. The other ligands all had scores below 5 and are even lower compared to sildenafil. Quercitrin also shows a "Yes" category in the AMES toxicity test, while the other ligands show a "No" category. For the hepatotoxicity category, only sildenafil showed a "Yes" category, and none of the ligands showed the same result.

Analysis related to pharmacokinetic features using the boiled egg model was conducted using SwissADME, with the analysis results presented in **Figure 11**. Five test ligands, namely puninic acid, kaempferol, quercetin, catechin, and ellagic acid, along with sildenafil, were found in the albumin (white) area, indicating better absorption in the digestive tract. The three other bioactive molecules are outside the boiled egg region.

Table 2. Pharmacokinetic and physicochemical parameters of ligands and standard PDE5 inhibitors (sildenafil).

Parameter	Cathechin	Ellagic acid	Garcinal	Garcinoic acid	Kaemp-ferol	Puninic acid	Quercetin	Quercitrin	Sildenafil
Molecular formula*	$C_{15}H_{14}O_6$	$C_{14}H_6O_8$	$C_{27}H_{39}N_2O_3+$	$C_{26}H_{34}IN_2O_4+$	$C_{16}H_{11}O_6+$	$C_{19}H_{33}N_3O_2++$	$C_{16}H_{11}O_7+$	$C_{24}H_{24}O_{11}++++$	$C_{22}H_{30}N_6O_4S$
Molecular weight* (g/mol)	290.7	302.19	439.61	565.46	299.25	335.48	315.25	488.44	474.58
Lipophilicity* (logP)	0.083	1	1	1	0.91	0.91	0.81	-7.31	1.94
Number of H-bond acceptors*	6	8	5	6	6	5	7	11	8
Number of H-bond donors*	5	4	2	2	3	2	4	5	1
Molar refractivity*	74.33	75.31	135.3	145.1	80.95	104.21	82.97	126.36	134.56
Topological polar surface area (TPSA)*	110.38	141.34	82.74	99.81	107.97	85.87	128.20	165.12	121.80
Solubility*	soluble	soluble	soluble	soluble	slightly soluble	slightly soluble	slightly soluble	slightly soluble	soluble
Gastro-	high	high	high	high	high	high	high	low	high

Parameter	Cathechin	Ellagic acid	Garcinal	Garcinoic acid	Kaemp-ferol	Puninic acid	Quercetin	Quercitrin	Sildenafil
intestinal absorption*									
Blood-brain barrier permeation*	no	no	no	no	no	no	no	no	no
Number of Lipinski's rules of 5 violated*	0	0	0	0	0	0	0	1	0
Biological availability score*	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55
Synthetic accessibility*	3.5	3.17	3.17	3.17	3.25	3.25	3.34	5.41	3.95
Median lethal dose (LD50**) (mol/kg)	1.787	2.416	2.446	2.544	2.371	1.945	2.582	2.369	2.655
Ames toxicity	no	no	no	no	no	no	yes	no	no
Hepato-toxicity*	no	no	no	no	no	no	no	no	yes

Note:*analysed with SwissADME web server
**analysed with pkCSM-pharmacokinetics web server

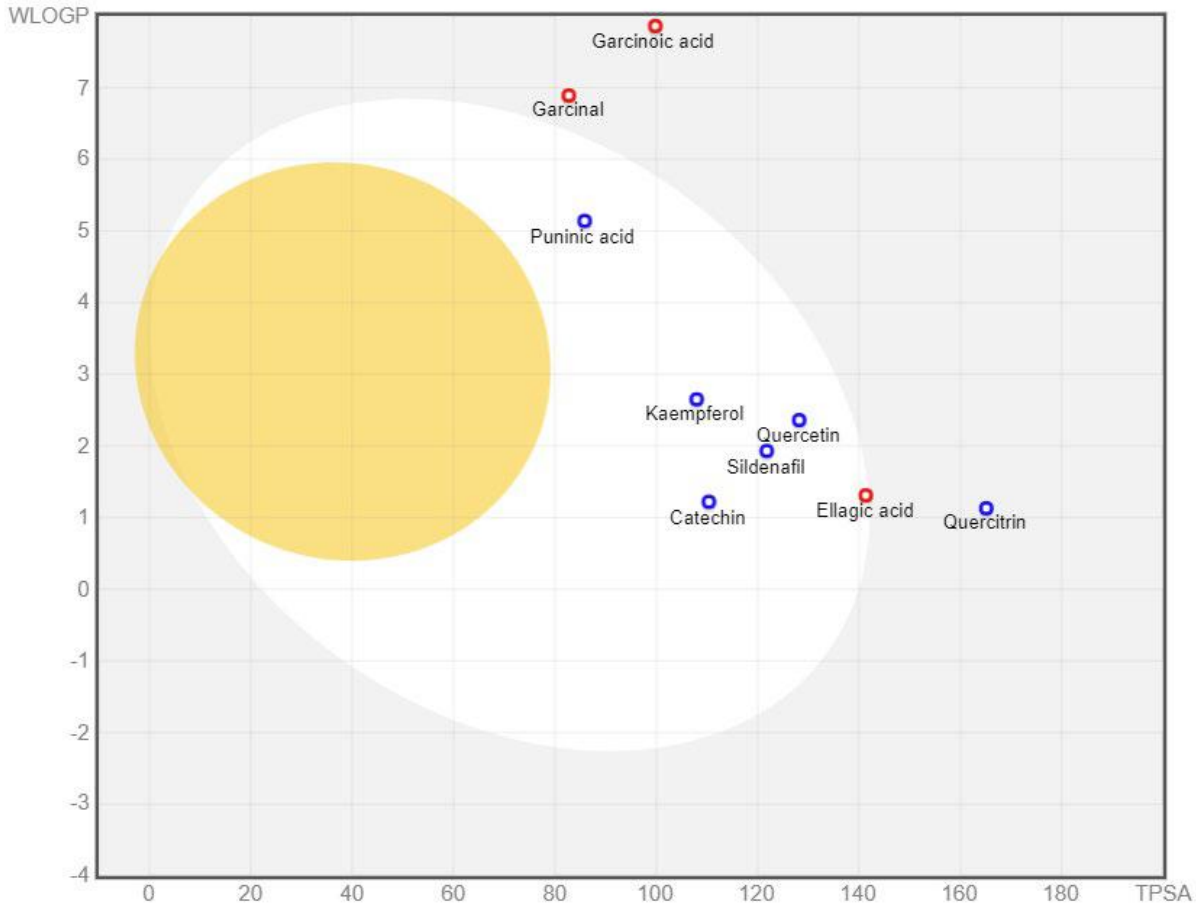

Figure 11. Boiled-egg model for test ligands and standard PDE5 inhibitor (sildenafil)

DISCUSSION

In this study, molecular docking was used to find effective bioactive molecules from several plants that are widely found in Indonesia and other parts of the world and have been utilized to treat ED, namely chives (*A. tuberosum*), nutmeg (*M. fragrans*), moringa (*M. oleifera*), velvet bean (*M. pruriens*), *G. kola*, and pomegranate (*P. granatum*), based on the calculation of their binding affinity to the target protein (PDE5) (Fauzi et al., 2019). The pharmacokinetic and physicochemical properties of the test compounds from these plants were also evaluated.

To identify the binding affinity of the test ligands with the receptor, each ligand was docked with the active site of PDE5 using the AutoDock Vina program. This computer program is an open-source program for molecular docking that uses a new scoring function and search algorithm to estimate protein-ligand affinity and predict binding modes. The scoring function is based on the X-Score function that uses empirical calculations to estimate the free binding energy. The search algorithm used in the docking process employs gradient optimization methods with a Lamarckian genetic algorithm to explore the conformational space of the ligands and proteins. The docking scores in the form of free binding energy of the test compounds were compared with the standard ED drug (sildenafil). The tested ligands showed docking scores ranging from -5.9 kcal/mol to -8.8 kcal/mol. Of the eight test ligands, only two ligands (garcinal and puninic acid) had free binding energies greater than the standard drug (sildenafil), while

kaempferol showed the same free binding energy as PDE5. Research by Rampogu et al. (2022) proves that the docking score reflects the activity of the inhibition of ligands in protein-ligand complexes.

Among the ligands tested with molecular docking in this study, 5 ligands (quercitrin, quercetin, garcinoic acid, ellagic acid, and catechin) were found to have a higher affinity for PDE5 compared to sildenafil, as evidenced by lower free binding energy values compared to PDE5. These ligands have specific chemical structures, characterized by a higher number of hydrogen bonds, compared to the test ligands with lower affinity. For example, quercetin, which has the highest affinity value along with quercitrin, has 5 hydrogen bonds compared to garcinal and punicic acid, which only have 1 hydrogen bond. The number of hydrogen bonds may contribute to stronger interactions with the PDE5 receptor. Therefore, the findings in this study indicate that most of the test ligands are likely to have relatively better inhibition activity than the standard drug (sildenafil).

Findings by Iwaloye et al. (2020) show that for inhibition to occur at the catalytic domain of PDE5, there must be hydrogen bonds and hydrophobic interactions with GLN817, non-polar interactions formed with PHE820 and VAL782, as well as contacts with HIS613, LEU765, and PHE786. This study reveals that almost all test ligands interact with HIS613, LEU765, VAL782, and PHE820. The interactions between these ligands and the PDE5 receptor are characterized by high hydrophobicity and a significant number of electron acceptors and donors, with the presence of alkyl, pi-alkyl, and C-H bond interactions (Iwaloye et al., 2020). Detailed studies show that four ligands, namely garcinal, ellagic acid, quercetin, and quercitrin, form π-π arrangements with PHE820. Pi-pi interactions are a type of non-covalent interaction that is important for biological events such as protein-ligand recognition by contributing to a significant amount of binding enthalpy (Iwaloye et al., 2020). In addition, all ligands also form hydrogen bonds and van der Waals interactions with key amino acid residues present at the PDE5 binding site. Research has demonstrated the importance of hydrogen bonds in evaluating ligand binding specificity (Gottschalk et al., 2016). The findings in this study reveal that the test ligands have interactions with the same key residues as sildenafil and indicate that this active substance has inhibition properties against PDE5 similar to sildenafil.

One of the most important components in drug discovery involves assessing the efficacy and toxicity of new drug candidates. The lack of efficacy and safety of drugs are two main causes of drug failure (Siramshetty et al., 2016). Therefore, the absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of chemicals play an important role at every stage of drug discovery and development (Siramshetty et al., 2016). A number of methods and tools have been developed to assess the physicochemical properties of a molecule that can influence pharmacokinetic and pharmacodynamic properties. In this study, the relevant physicochemical and pharmacokinetic properties of the selected ligands were predicted using the SwissADME web server and pkCSM-pharmacokinetics. Lipinski's rule of five (ROF) is one of the parameters required before a compound is considered a drug candidate (Lipinski et al., 2012). According to Lipinski et al. (2012), compounds with drug-like attributes should not violate more than one of the following rules: molecular weight <500 Da, octanol-water partition coefficient <5, hydrogen bond donors ≤5, hydrogen bond acceptors ≤10. This study reveals that all ligands comply with the ROF. Furthermore, all ligands studied absorb well in the digestive system. In addition, there

are no test ligands that can penetrate the blood-brain barrier and the skin layer. Therefore, all test molecules have potential as drug candidates in terms of activity and pharmacological properties.

The boiled-egg model was used to further confirm the GI absorption properties and blood-brain barrier permeability of all ligands (Daina & Zoete, 2016). The visualization results from the model show that no test ligands can pass through the BBB, but all are in the area on the graph that indicates GI absorption capability. Five of the eight ligands are located in the part of the boiled egg white, indicating that these ligands are estimated to be absorbed passively by the digestive tract, while three ligands in the gray area are suspected to have low absorption and limited blood-brain barrier permeability (Daina & Zoete, 2016). Of the five ligands in the egg white area, only ellagic acid appears at the red point. This indicates that ellagic acid is estimated to undergo active efflux by P-glycoprotein (PGP+). Pgp (P-glycoprotein) is a transporter protein in cell membranes and plays a role in the absorption, distribution, and elimination of drugs in the body. The similarity of drugs and ADMET properties of the five ligands, namely catechin, quercetin, kaempferol, puninic acid, and ellagic acid, overall shows an identical pharmacokinetic profile to the reference drug (sildenafil), especially in terms of bioavailability and toxicity.

Among several widely found plants utilized in the treatment of ED, only *G. kola* contains catechin, a polyphenol-flavanol compound from the flavonoid family found in various plants, such as green tea, grapes, cocoa, vegetables, and algae (Justino et al., 2018; Ojo et al., 2021). High catechin content has also been found in fresh tea leaves, apricots, green beans, black grapes, strawberries, and soursop leaves (Justino et al., 2018). *Annona senegalensis*, a plant closely related to soursop (*Annona muricata*), has been reported as a plant with potential as a medicine for ED (Folawiyo et al., 2023). Thus, the utilization of tea leaves and soursop leaves, which are widely found in Indonesia, in the management of ED can be further researched.

Odubanjo et al. (2018) reported that extracts from nutmeg seeds (*M. fragrans*) and moringa seeds (*M. oleifera*) contain ellagic acid, quercetin, and kaempferol that show inhibitory effects on PDE5 enzymes. The results of this study confirm their findings. These three bioactive molecules have been proven through molecular docking analysis to have better affinity than the standard ED drug (sildenafil) against PDE5 and show drug similarity and ADMET properties similar to sildenafil. Nutmeg and moringa are plants that can be found throughout Indonesia and have been utilized to treat various disorders and diseases (Sabastian et al., 2015). The potential of these two plants as ED drugs is worthy of further investigation.

Pomegranate (*P. granatum*) is a well-known fruit worldwide and contains many bioactive compounds, including ellagic acid, puninic acid, and catechin (Carvalho Filho, 2014; de Oliveira et al., 2020). Pomegranate and its bioactive compounds have been widely utilized in health as antioxidant, anti-inflammatory, and antimicrobial drugs, as well as in the prevention and treatment of several chronic diseases (Goswami et al., 2014). Research shows that men who consume pomegranate juice daily for eight weeks experience a significant improvement in erectile function compared to the group receiving a placebo (Forest et al., 2007). Another study found that pomegranate juice increases sexual function in men with mild to moderate ED (Giménez-Bastida et al., 2021). Although these results are promising, further research is needed to confirm the effects of pomegranate on ED. The results of this study indicate that there are several

ligands with high affinity, even higher than sildenafil. Further analysis of the pharmacokinetic and physicochemical properties reveals that these ligands have drug-like similarities and ADMET properties similar to sildenafil. These findings open the potential for utilizing these plants as alternative natural PDE5 inhibitors.

In this study, there are several limitations that are important to clarify. Aspects such as limited sampling of ligand and receptor conformations in pose prediction, as well as the use of estimated scoring functions often result in data that is inconsistent with experimentally measured binding affinities. The inherent uncertainty in in silico studies, including molecular docking, demands careful interpretation of the findings in this research. Based on the results of this study, further research involving experimental validation and additional simulations, as well as in vitro or in vivo studies, is important to verify the efficacy of the ligands identified through in silico studies as PDE5 inhibitors.

CONCLUSION

This study found that there are ligands from herbal sources, namely pomegranate (*P. granatum*) containing ellagic acid and catechin, nutmeg (*M. fragrans*) and moringa (*M. oleifera*) containing ellagic acid, quercetin, and kaempferol, as well as *G. kola* containing catechin, which show potential as PDE5 inhibitors and have pharmacokinetic profiles comparable to sildenafil. Further research involving experimental validation through in vitro or in vivo studies is important to verify the efficacy of the ligands identified through in silico studies as PDE5 inhibitors.

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