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Research Article

Phytocompounds from Indonesia Medicinal Herbs as Potential Apelin Receptor Agonist for Heart Failure Therapy: An In-silico Approach

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Abstract: Heart failure is still a global health problem that demands new pharmacological treatments. The Apelin Receptor (APR), a class A (rhodopsin-like) G-Protein Coupled Receptor (GPCR), is one of the cell membrane receptors that potentially become a specific target of heart failure therapy when activated. However, no clinically approved drugs target APR. Phytochemical compounds from Indonesian herbs have become readily available for discovering novel apelin agonists. This study investigates bioactive phytochemicals from ten Indonesian medicinal herbs using computer-aided drug design (CADD) to predict ligand-receptor interactions via molecular docking and bioactivity prediction through machine learning. The selected herbs include *Andrographis paniculata, Centella asiatica, Zingiber officinale, Curcuma longa, Curcuma domestica, Morinda citrifolia, Guazuma ulmifolia, Orthosiphon stamineus, Moringa oleifera*, and *Garcinia mangostana*. Their pharmacokinetic and physicochemical profiles were also assessed using web-based predictions. Active metabolites were sourced from the Knapsack Database. Molecular docking using Molegro Virtual Docker assessed binding energy, with more negative MolDockScores indicating stronger interactions. Gambogic acid (-155.1 kJ/mol) from *Garcinia mangostana* and Procyanidin B2 (-154.5 kJ/mol) from *Guazuma ulmifolia* exhibited stronger binding than the APR agonist, Azelaprag (-149.9 kJ/mol). This study showed that Gambogic acid, Procyanidin B1, and Procyanidin B2 may predict excellent half maximal effectivity (EC50) against apelin receptors, despite their unideal lipophilicity-ligand efficiency (LELP). Gambogic acid demonstrated favorable pharmacokinetic properties: good bioavailability, minimal blood-brain barrier penetration, no cytochrome P450 (CYP) enzyme interactions, and low toxicity. The study concluded that all five selected compounds exhibited strong interactions and bioactivity as APR agonists, supporting the need for further validation through in-vitro studies.

Keywords: Apelin receptor; Apelin receptor agonist; Heart failure; Indonesia medicinal herbs; *In-silico*

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1. Introduction

Heart failure remains a significant global health challenge, affecting 1-2% of the global population (Savarese et al., 2023). Southeast Asia, particularly Indonesia, accounts for 900 cases per 100.000 population (Feng et al., 2024). Although established heart failure drugs have significantly improved patient outcomes (McDonagh et al., 2021), their side effects and contraindications limit their universal applicability (Ahmad et al., 2023; Koçak et al., 2023; Davin et al., 2019). This underscores the urgent need for novel targets and safer, more effective alternative therapies.

One promising target in the search for new heart failure treatments is the Apelin Receptor (APR), a class A G-Protein Coupled Receptor (GPCR) (Yue et al., 2022; Rossin et *al.*, 2023). Previous research has shown that activating APR can lead to substantial improvements in cardiac function, as demonstrated in both human and animal models of heart failure (Winkle et al., 2023; Chapman et al., 2023). The beneficial effects of the Apelin receptor are likely due to mechanisms such as enhancing nitric oxide (NO)-dependent signaling, counteracting Angiotensin-II (Ang-II) and Ang-II 1 Receptor (AT1R) activation, repressing transforming-growth factor-β (TGF-β), and activating extracellular signal-regulated kinase 1/2 (ERK1/2), which enhances myocardial contractility (Song et al., 2022). Despite its potential, no clinically approved drugs currently target this receptor.

Phytochemical compounds derived from herbs, known for their drug-like properties, offer a promising avenue for discovering anti-heart failure drugs (Nasiruddin, 2022; Shah et al., 2019), especially through APR. With its rich biodiversity and vast array of plant species, Indonesia presents a unique opportunity to explore natural metabolites for pharmaceutical development. The country's abundant flora could yield potential candidates for heart failure treatment by leveraging the therapeutic potential of native medicinal herbs. *In-silico* studies, such as molecular docking (Hakim et al., 2023; Husnawati et al., 2023; Sahlan et al., 2020) combined with machine learning or artificial intelligence(Ahmed et al., 2024; Heryanto et al., 2023), are cost- and time-effective methods that can efficiently identify promising compounds before they undergo *in-vitro* testing (Roney and Mohd Aluwi, 2024). Previous studies have also approached how the apelin receptor agonist finds its potential cardiovascular beneficial effect (Portilla-Martinez et al., 2022; Tran et *al.,* 2021). However, among available published reports, no such publications explicitly have reported *in-silico* screening of bioactive compounds from Indonesian medicinal herbal to test their potential as APR agonists. While the use of in-silico techniques for high-throughput screening is well established, previous studies have also clearly defined the use of lipophilicity metrics to normalize bioactivity when identifying potential apelin receptor agonists. Therefore, this study aims to harness the bioactive compounds found in Indonesian plants to identify new, effective APR agonists for combating heart failure using *in-silico* methods.

2. Methods

2.1. Compound Acquisition and Drug-likeness Properties

For this preliminary in-silico study, we selected ten herbs commonly found in Indonesia that are known for their cardioprotective properties. These herbs were chosen based on their empirical use as traditional medicine among Indonesians. These herbs include *Andrographis paniculata* (Eziefule et al., 2024; Tian et al., 2023; Wang et al., 2022), *Centella asiatica* (Fadhillah et al., 2024; Ding et al., 2022; Bunaim et al., 2021), *Zingiber officinale* (Hosseini et al., 2024; Zhu et al., 2021), *Curcuma longa* (Akhter and Nahar 2022; Pourbagher-Shahri et al., 2021), *Curcuma domestica* (Pourbagher-Shahri et al., 2021), *Morinda citrifolia* (Oluwafemi et al., 2023), *Guazuma ulmifolia* (Ramadhansyah et al., 2023; Dos Santos et al., 2018), *Orthosiphon stamineus* (Mohmad Saberi and Chua 2023), *Moringa oleifera* (Alia et al., 2022; Louisa et al., 2022), *and Garcinia mangostana* (Soetikno et al., 2020; Elmund and Hartrianti 2020). We choose all of these herbs based on empirical use as traditional medicine among Indonesian. The bioactive compounds from these herbs were identified using the KNApSAcK database (http://www.knapsackfamily.com/knapsack_core/top.php

As for screening and preliminary purposes, we selected 4-8 compounds for each herb in this database based on (1) drug-likeness profile through SwissADME, (2) previous research evidence that the compound has promising bioactivity, and (3) the presence in the KNApSAcK as known constituents in selected herbs. As long as the compound is present in KNApSAcK with one of the other two criteria, we included the compound in this study. E Furthermore, the Chemical Abstracts Service Identifier (CAS-ID) for each included compound was retrieved, and the compounds were inputted into PubChem (https://pubchem.ncbi.nlm.nih.gov/) to obtain their canonical Simplified Molecular Input Line Entry System (SMILES) for molecular docking. It is a notation that allows a user to represent a chemical structure in a way that can be used by various software programs to perform molecular modeling, database searches, and other computational chemistry tasks. The study protocol is summarized in Figure 1.

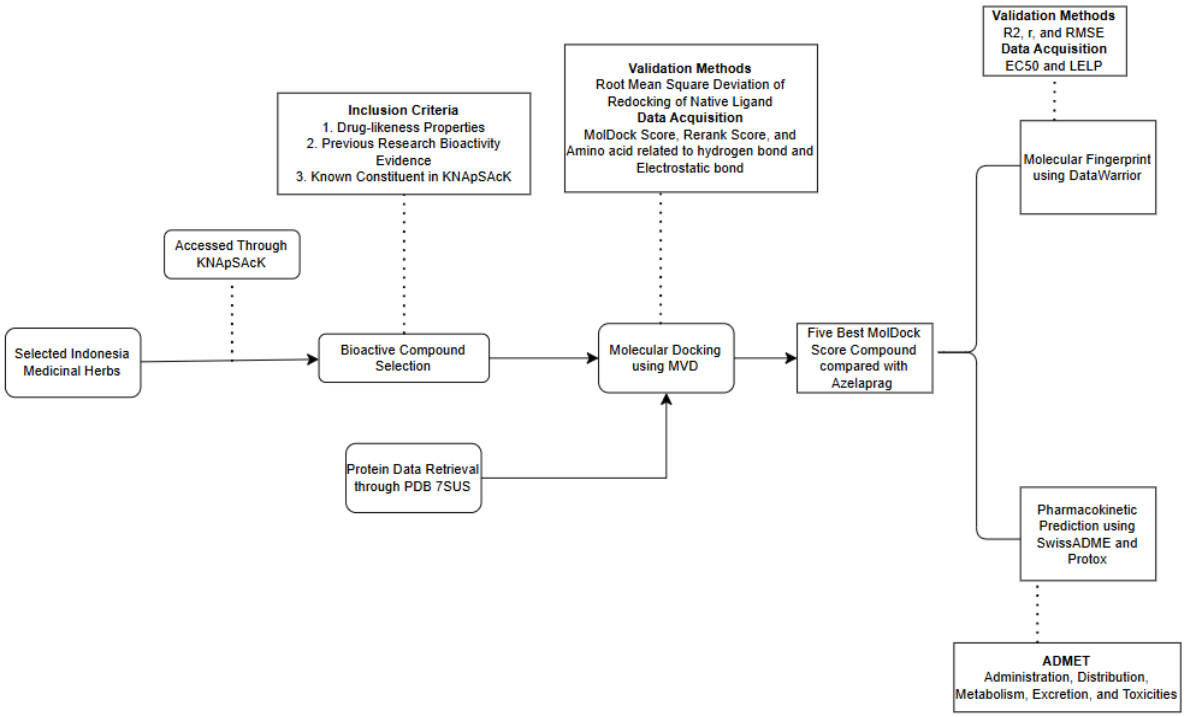


Figure 1 Overview of Study Protocols

Subsequently, the drug-likeness of these compounds was predicted through SwissADME SwissDrug Design (http://www.swissadme.ch/) (Hernandez et al., 2024), based on Lipinski's Rule of Five. Drug-likeness refers to the qualitative aspect of a specific compound that has the potential to become a drug based on its structural, physiochemical, and pharmacokinetic properties. Lipinski's Rule of Five evaluates a compound's drug-likeness based on four criteria—molecular weight less than 500 Daltons, no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, and a LogP less than 5—to predict its suitability for oral bioavailability and stability (Hakim et al., 2023). Drug-likeness refers to the evaluation of a compound's properties to determine its suitability for development as a drug.

2.2. Molecular Docking Analysis of Selected Compound

Molecular docking is a technique used to evaluate the ability of compounds to interact with the active site of specific proteins by studying the ligand-receptor atom-atom interaction (Zothantluanga and Chetia, 2022). In this study, Molegro Virtual Docker (MVD) (free trial version) was utilized for this purpose (Dwira et al., 2024). The apelin receptor (Protein Data Bank/PDB: 7SUS) was retrieved from the Research Collaboratory for Structural Bioinformatics (RSCB) PDB (https://www.rscb.org), along with its native ligand. Validation of the docking process was

performed by setting the active site center at coordinates X: -41.09, Y: 5.46, and Z: 50,51 with a radius of 10 Å, based on redocking the native ligand and achieving a Root Mean Square Deviation (RSMD) <2.0 after energy minimization. The specificity of the active site was further confirmed through the Computed Atlas of Surface Topography of Proteins (CASTp) website (http://sts.bioe.uic.edu/castp/index.html?3trg) to determine its specific position, as previously described (Husnawati et al., 2023; Sahlan et al., 2020). Binding interactions were assessed using MolDockScore and ReRank Score and analyzed for hydrogen bonding and electrostatic interactions between each compound and the apelin receptor's active site. Two-dimensional (2D) and three-dimensional (3D) visualizations were generated for the top five compounds which exhibited the most negative binding energies. The docking results were compared with those of azelaprag, a known apelin receptor agonist, to establish a benchmark (Winkle et al., 2023). The computer used for performing molecular docking has Window 11 operating system with an Intel® Core™ i7-8665U CPU@1.90 GHz -2.11 processor with RAM 16 GB (Dwira, et al, 2024).

2.3. Bioactivity Prediction Analysis

After selecting the top five molecules for interaction with the Apelin Receptor (APR), we conducted a further assessment of their bioactivity utilizing machine learning techniques through molecular fingerprint analysis (MFP). defined as MFP utilizing a molecular descriptor known as SkelSpheres, analyzed via the array binner provided by DataWarrior® software, and identified patterns using support vector regression (SVR) (Heryanto et al., 2023). For this study, we focused on predicting the bioactivity of the compound. Bioactivity is defined as the ability of a certain substance to produce a biological effect on living tissue, cells, or organisms, which might be inhibitory activity or enhancement activity. In this research, we tried to predict the half-maximal effective concentration (EC_{50}), which represents the concentration required to achieve 50% of the maximum biological activity, as provided by the ChEMBL database. This database provides a comprehensive and publicly accessible database that contains information on bioactive molecules with drug-like properties. The EC_{50} values for the isolated compound were categorized using established criteria (Indrayanto et al., 2021). To account for the variability in EC_{50} data, as it might be varied and complex from one in-vitro data to another, we also predicted lipophilicity-ligand efficiency (LELP, Equation 1), which normalizes the high variance of predicted compounds. LELP measures bioactivity by correcting ligand efficiency for lipophilicity and other physicochemical properties of the compound, including cLogP, LE (Equation 2 and 3), HA, and pEC50, with an optimal range of ideal drugs between 0 and 7.5 units (Leeson et al., 2021; Kenny, 2019). Below is the formula for determining LELP, which is computed automatically by DataWarrior:

$$LELP = \frac{cLogP}{LE} \quad (1)$$

$$LE = \frac{1.37}{HA} * pEC50 \quad (2)$$

$$LE = \left(-2.303\left(\frac{RT}{HA}\right)\right) * LogKd \quad (3)$$

where

cLogP : Partition Coefficient which reflect ratio between the concentration of a substance in two different polarity solvents

LE : Ligand Efficiency, binding energy per atom of a ligand to the receptor

HA : Heavy Atom or non-H atom on molecules

pEC50 : Log EC50

R : Ideal Gas Constant 1.987×10^{-3} kcal/K/mol

T : Temperature (K, Kelvin)

Data available in DataWarrior® was divided into training and testing datasets using clustering methods, with a similarity threshold of 0.9 for the SkelSpheres Descriptor. Compounds within the

training dataset were used to build the model, while those in the testing dataset were used for validation. EC_{50} values were transformed into Log EC_{50}, and LELP values were derived from the EC_{50} inputs within the software. This validation approach followed methodologies outlined in previous studies (Heryanto et al., 2023). Model performance was evaluated using R-squared (R^2), root mean square error (RMSE), and Spearman's rank correlation coefficient (Gramatica, 2020; Heryanto R et *al.,* 2023). Predictions for bioactivity were also made for the standard drug, azelaprag, which has been tested in the human study (Winkle et al., 2023).

2.4. Physiochemical Radar, Pharmacokinetic, and Toxicity Prediction Analysis

The five molecules with the best molecular docking results, characterized by more negative binding energies, were selected for further analysis of their physiochemical properties, pharmacokinetics, and toxicity. Physiochemical radar predicts certain features that represent the physical and chemical characteristics of certain compounds, whereas pharmacokinetic profile is a parameters that study how the compound or drug moves through the body over time. Using their canonical SMILES representations, the pharmacokinetic properties, including absorption, distribution, metabolism, excretion, and toxicity, are predicted using SwissADME Swiss Drug Design (Hernandez et al., 2024) (http://www.swissadme.ch/) and Protox 3.0 (https://tox.charite.de/protox3/?site=compound_input) (Banerjee et al., 2024). Additionally, these predictions were performed for azelaprag, which served as a standard drug for comparison. (Winkle et al., 2023).

3. Results and Discussion

3.1. Selected Tested Compound and Drug-Likeness

Figure 2 summarizes the characteristics of the selected compounds, including their drug-likeness properties, using Lipinski's Rule of Five. In this study, a total of 69 compounds were evaluated for their potential binding activity to apelin receptors. Among these, Procyanidin B1 and Procyanidin B2 were found to have three violations of Lipinski's criteria, indicating that they may not be ideal candidates for oral drug development. Since previous studies mentioned their cardioprotective effect, we chose them in the analysis. As an additional insight, some studies have shown that some molecules with high molecular weight or suboptimal physiochemical properties can still exhibit good bioavailability, potentially enhanced by chemical modifications or the use of absorption enhancers (Asano et al., 2024).

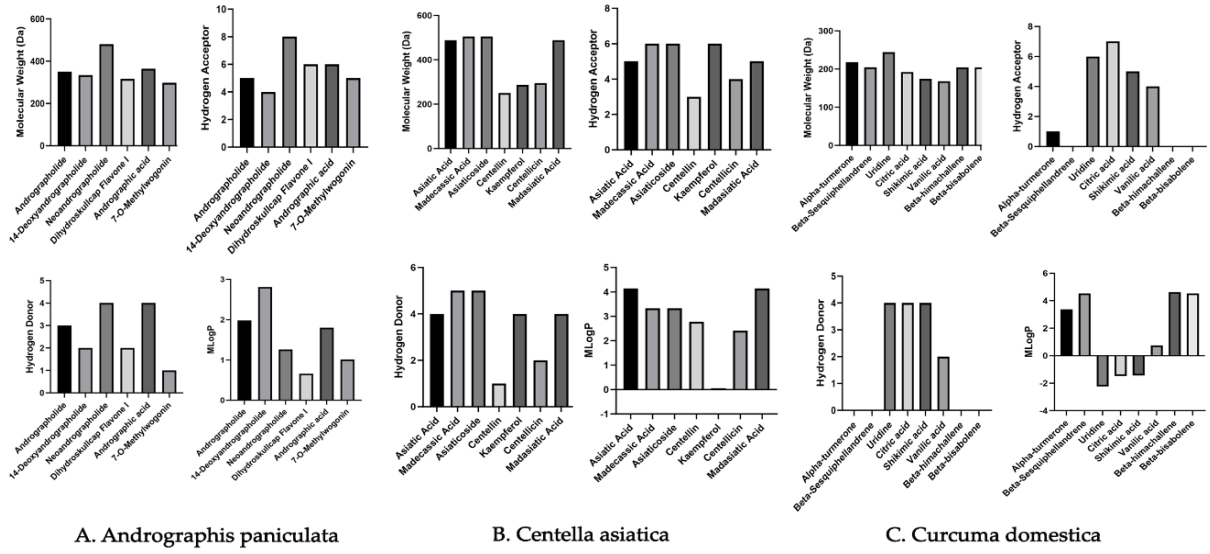
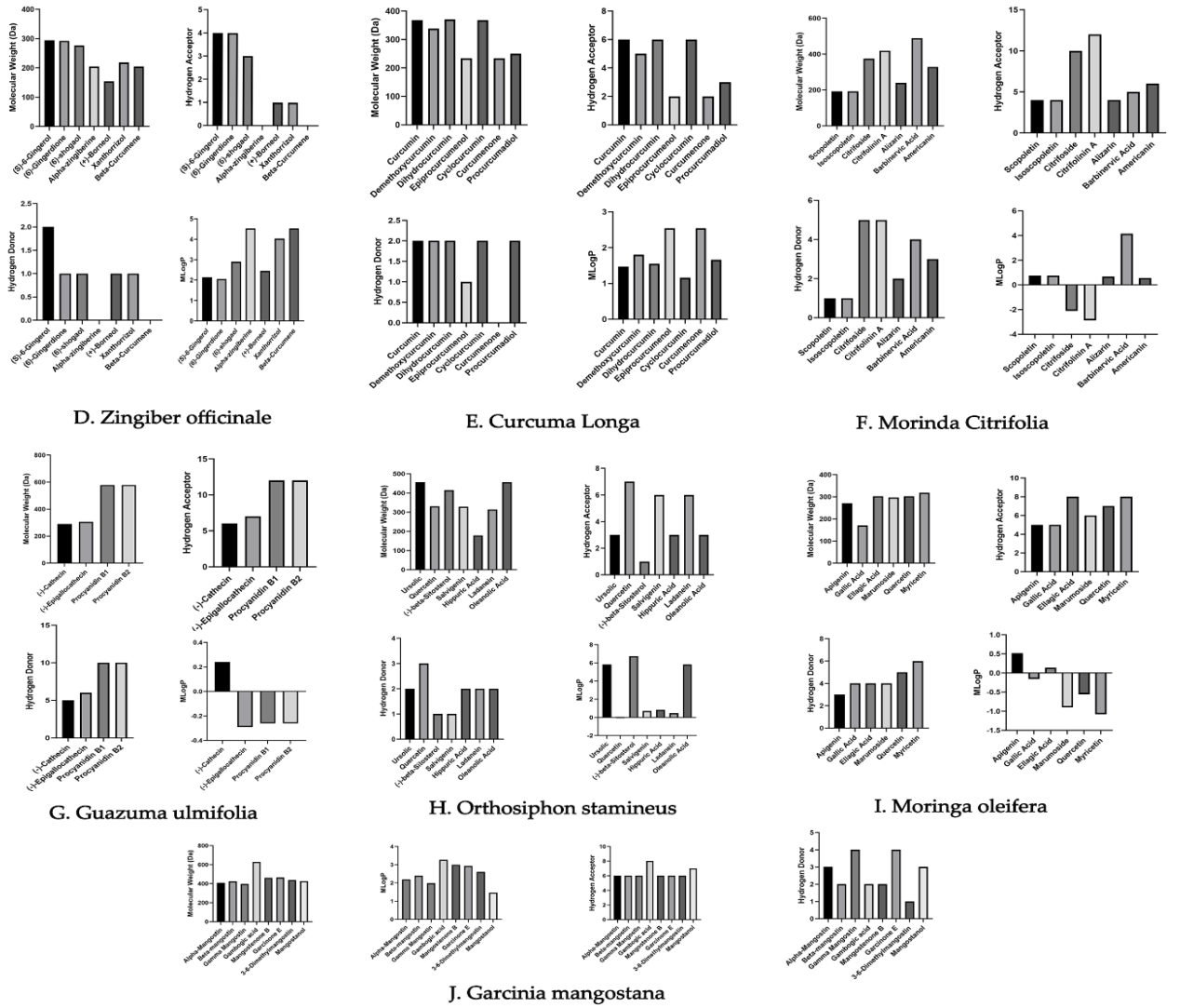


Figure 2 Selected Bioactive Compounds and Drug Likeness Properties (A) *Andrographis paniculata,* (B) *Centella asiatica*, (C) *Curcuma domestica,* (D) *Zingiber officinale*, (E) *Curcuma longa,* (F) *Morinda citrifolia,* (G) *Guazuma ulmifolia,* (H) *Orthosiphon stamineus*, (I) *Moringa*

oleifera, and (J) Garcinia mangostana (Cont.). where MW: Molecular Weight; HA: Hydrogen Acceptor; HD: Hydrogen Donor; MLogP : Moriguchi Logarithm of the octanol/water partition coefficient



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3.2. Molecular Docking Studies

In this study, binding energy was assessed using MolDock Scores to evaluate the binding potential of each tested compound (Dwira et al., 2024). To ensure validity, the redocking of the native ligand demonstrated similar binding poses, with a Root Mean Square Deviation (RMSD) of 0.58 Å. Figure 3 displays the native ligand both before and after redocking. The native ligand exhibited a MolDock Score of -186.5 Kj/Mol and a Rerank Score of -145.2 Kj/Mol. Hydrogen bonding was primarily observed with residues Tyr264 and Lys268.

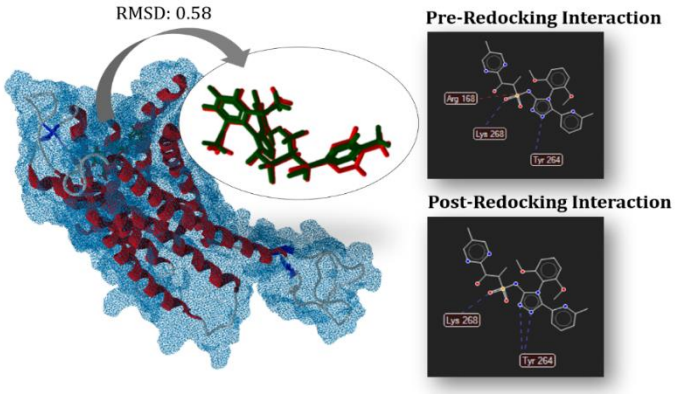

Figure 3 Validation Docking Methods Using Redocking of Native Ligand from PDB 7SUS. This figure illustrates the validation of the docking methodology through the redocking of the native ligand from PDB entry 7SUS. It shows a comparison of binding poses before and after redocking to confirm the accuracy and reliability of the docking protocol

All 69 compounds demonstrated negative binding energies, indicating that they interact spontaneously with the active site. Detailed results of the entire molecular docking study are provided in the **Supplementary Material**. Notably, Gambogic acid (-155,1 Kj/Mol) and Procyanidin B2 (-154,5 Kj/Mol) exhibited lower MolDock Scores compared to Azelaprag (-149.9 Kj/Mol) (see Table 1). Following these, the next three compounds were Asiaticoside (-147,5 Kj/Mol), Procyanidin B1 (-145,8 Kj/Mol), and Dihydrocurcumin (-137,2 Kj/Mol). Gambogic acid, Procyanidin B2, and Asiaticoside formed hydrogen bonds at Arg168, similar to Azelaprag, while Procyanidin B2 and Dihydrocurcumin interacted with Lys268. In contrast, Procyanidin B1 formed hydrogen bonds with Met183 and Glu198, differing from those of Azelaprag (Figure 4).

Hydrogen bonding is a crucial interaction mechanism in biological systems, particularly in ligand-receptor interactions. Although compounds with lower negative binding energies may still be effective, a greater number of hydrogen bonds can help mitigate the development of drug resistance phenomenon (Zothantluanga and Chetia, 2022). Among the top five compounds, two compounds, Asiaticoside forms five hydrogen bonds with Arg168, Gln180, Met183, Glu198, and Tyr299, while Procyanidin B1 forms four hydrogen bonds with Ser105, Arg168, Cyr181, and Lys268.

Table 1 Molecular Docking Results of Top Five Compounds

Compound	MolDockScore (kJ/mol)	Rerank Score (kJ/mol)	Hydrogen Bond (kJ/mol)	Amino Acid Related to Hydrogen Bond	Amino Acid Related to ElectroStatic Bond
Gambogic acid	-155.1	-65.7	-2.9	Tyr88, Arg168	Trp85, Tyr88, Ile109, Phe110, Arg168, Cys181, Phe291
Procyanidin B2	-154.5	-115.03	-5.1	Ser105, Arg168, Cys181, Lys268	Tyr88, Ile109, Ser106, Arg168, Phe291
Azelaprag	-149.9	-100.3	-7.6	Ser106, Arg168, Lys268	Trp85, Ile109, Arg168, Met183
Asiaticoside	-147.5	-38.8	-15.7	Gln180, Met183, Arg168, Tyr299, Glu198	Phe78, Trp85, Arg168, Tyr182, Tyr185, Tyr264, Lys268, Met288, Thr295
Procyanidin B1	-145.8	-77.5	-9.7	Met183, Glu198	Lys268, Phe291
Dihydrocurcumin	-137.2	-111.4	-10.4	Lys268, Leu287, Ser298	Tyr264, Lys268, Met288, Phe291, Tyr299

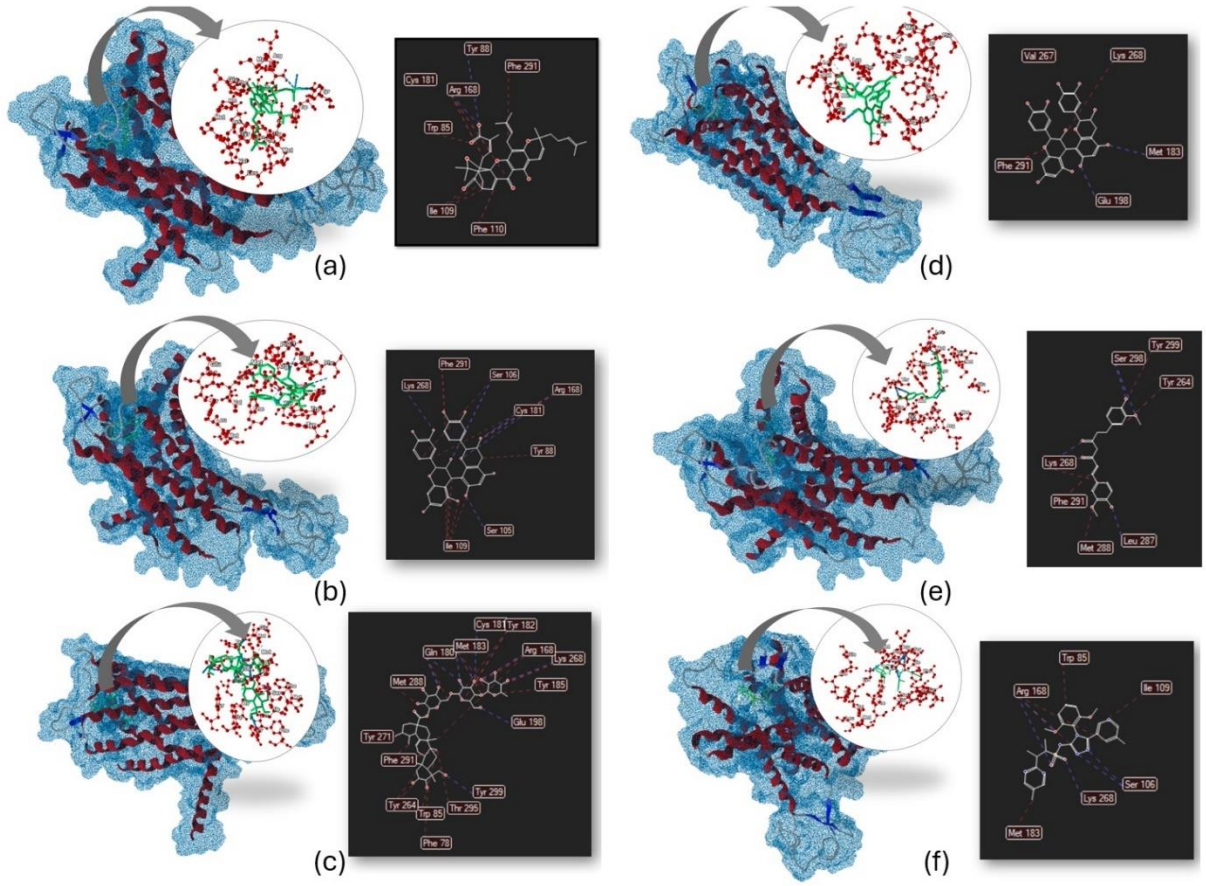

Figure 4 2D and 3D Visualization of Selected Compound Against Apelin Receptor PDB 7SUS. (a) Gambogic Acid, (b) Procyanidin B2, (c) Asiaticoside, (d), Procyanidin B1, (e) Dihydrocurcumin, and (f) Azelaprag. The figure provides both two-dimensional and three-dimensional representations of these compounds in complex with the Apelin Receptor to illustrate their binding interactions

3.3. Bioactivity Prediction Analysis Results

EC_{50} is a critical parameter used in preclinical assays to evaluate the concentration of a compound required to achieve 50% of its maximal effect on a specific signaling pathway (Indrayanto et al., 2021). LELP integrates bioactivity with physicochemical properties, such as LogP, to enhance the identification of promising drug candidates. Compounds with favorable LELP values are expected to exhibit beneficial **a**bsorption, **d**istribution, **m**etabolism, **e**xcretion, and **t**oxicity (ADMET) characteristics (Leeson et al., 2021; Kenny 2019). For statistical analysis, R^2 (with a value greater than 0.5) (Catalani et al., 2021), root mean square error (RMSE, should be low), and Spearman's rank correlation coefficient (r) were computed using GraphPad® Software (Gramatica 2020). In this research, a total of 898 EC_{50} data were extracted from the ChEMBl database. The compounds were clustered based on their similarity, resulting in 90 compounds designated as test data and 808 compounds as training data **(See Supplementary Materials)**. Validation of the EC50 data on the training set revealed an R^2 below 0.5, indicating an inadequate model fit. Nonetheless, the model demonstrated practical accuracy with a low RMSE and a strong linearity (r=0.62). Conversely, the LELP model exhibited excellent fit and very strong linearity, despite a high RMSE) (see Figure 5). It is important to note that the model should exhibit strong linearity, as indicated by an R^2 value above 0.5, along with high correlation coefficients, which reflect the strength of the relationship between the X and Y variables.

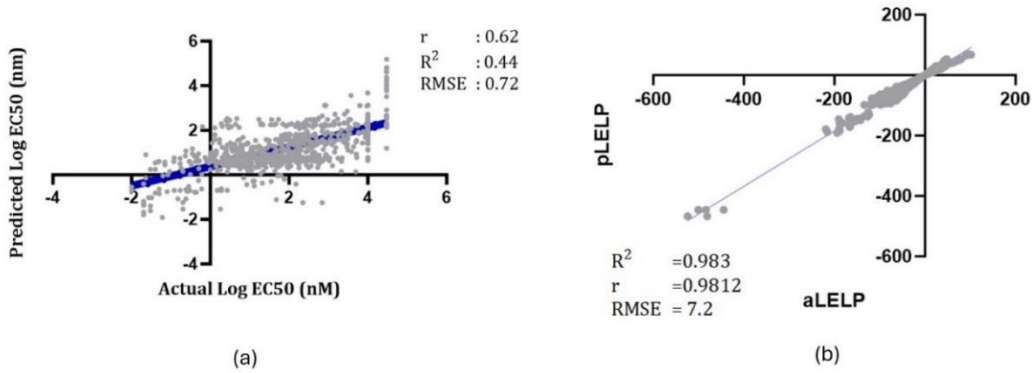

Figure 5 Validation of Machine Learning Models. This figure displays the performance metrics for model validation, including RMSE (Root Mean Square Error), R^2 (Coefficient of Determination), and r (Spearman Correlation Coefficient). These metrics evaluate the accuracy and reliability of machine learning models

Based on our bioactivity results, the Gambogic acid, Procyanidin B1, Procyanidin B2, and dihydrocurcumin exhibited potent activity (pEC_{50} <1 µM) as APR inducers, comparable to Azelaprag (see Table 2). In contrast, Asiaticoside shows good activity (pEC_{50} 2.5 µM), falling into the 1-20 µM range. For hit identification, all compounds displayed unfavorable LELP values (>7.5), unlike Azelaprag, which has an LELP of 7.29. Gambogic acid, Procyanidin B1, Procyanidin B2, and Asiaticoside have a high molecular weight (>500 Kda), contributing to their less favorable scores. Dihydrocurcumin, despite meeting Lipinski's Rule of Five, shows comparable LELP values to Procyanidin B1 and B2. This discrepancy may be attributed to Dihydrocurcumin's EC_{50} being ten times higher than that of Procyanidin B1 and B2, impacting its LELP score (Indrayanto et al., 2021; Leeson et al., 2021; Kenny, 2019). An unfavorable LELP value is generally associated with reduced binding affinity of ligands to their target proteins. (Leeson et al., 2021; Kenny 2019) However, it is worth noting that there is an increasing trend of U.S. Food and Drug Administration (FDA)--approved orally bioavailable drugs with intermediate to large molecule sizes, often utilizing the "extended" Rule of Five (Viarengo-Baker et al., 2021) or alternative methodologies such as the Active Biopharmaceutical Molecule Profiling System (AB-MPS), as suggested by DeGoey et *al.,* (Degoey et al., 2018).

Table 2 Bioactivity Prediction of Top Five Compounds

Name of Compound	Predicted EC_{50} (µM)	Predicted LELP	Category (EC_{50} and LELP)
Gambogic Acid	0.06	35.0	Excellent Activity, Unideal
Procyanidin B1	0.01	8.8	Excellent Activity, Unideal
Procyanidin B2	0.01	8.8	Excellent Activity, Unideal
Dihydrocurcumin	0.11	8.6	Excellent Activity, Unideal
Asiaticoside	2.57	-3.1	Good Activity, Unideal
Azelaprag	0.002	7.3	Excellent Activity, ideal

3.4. Oral Bioavailability Radar, Pharmacokinetic, and Toxicities Prediction Analysis

SwissADME provided an Oral Bioavailability Radar that evaluates six key physiochemical parameters for assessing drug candidates' oral bioavailability. The radar features include (1) Lipophilicity: Ideal range is -0.7 < XLogP < +5.0; (2) Size: Optimal molecular weight range is 150 < Molecular Weight < 500 Da; (3) Polarity: Ideal range for Topological Polar Surface Area (TPSA) is 20 Å² < TPSA < 130 Å²; (4) Insolubility: Desired range is -6 < Log S(ESOL) < 0; (5) Insaturation: Fraction of sp^3 hybridized carbon atoms should be between 0.25 and 1; and (6) Flexibility: Optimal

number of rotatable bonds is between 0 and 9. The Oral Bioavailability Radar for each compound is illustrated in Figure 6. The analysis revealed that only Dihydrocurcumin exhibited favorable physiochemical properties, suggesting good oral bioavailability. This is consistent with research suggesting that formulation modifications can enhance bioavailability. Furthermore, chemical modifications and the use of absorption enhancers are well-established strategies for improving the absorption of drug candidates (Asano et al., 2024; Wibowo et al., 2021).

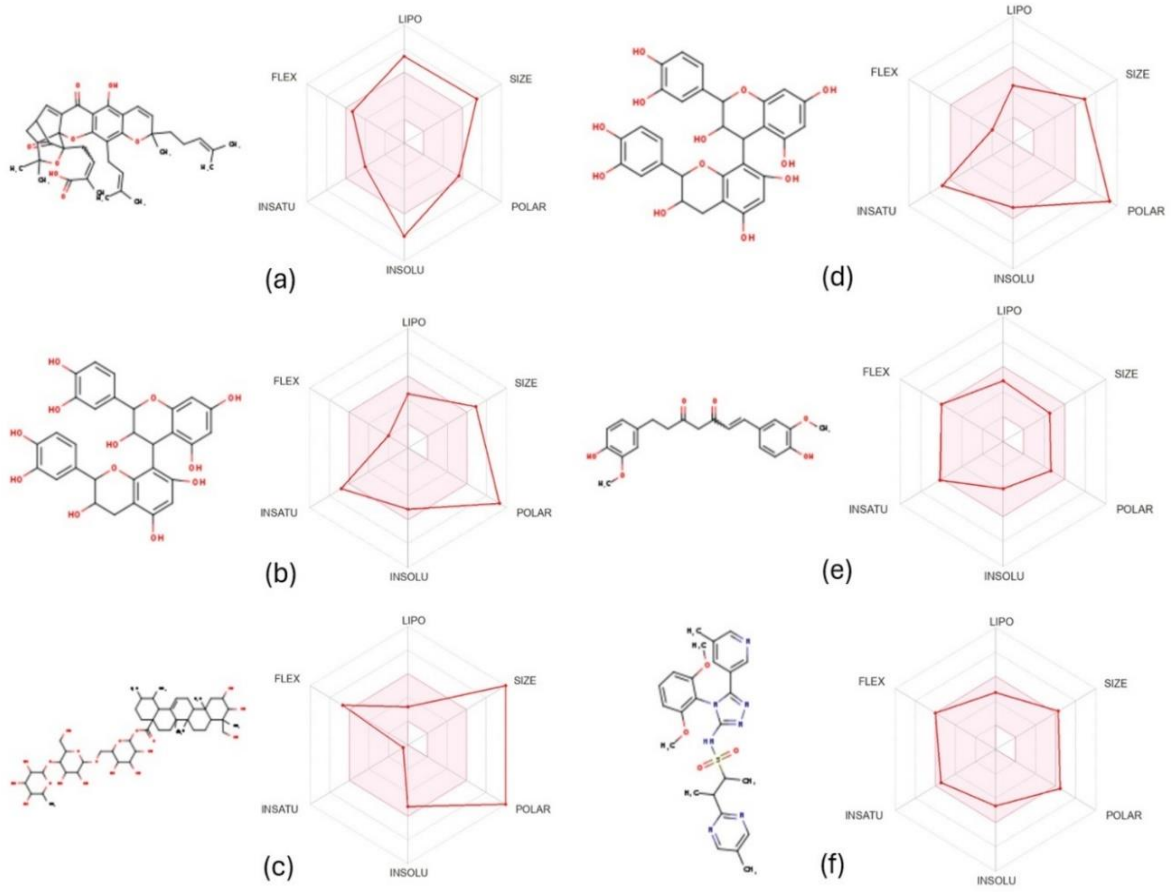

Figure 6 Oral Bioavailability Radar for Selected Compounds. This figure displays the Oral Bioavailability Radar for the following compounds: (a) Gambogic Acid, (b) Procyanidin B1, (c) Asiaticoside, (d) Procyanidin B2, (e) Dihydrocurcumin, and (f) Azelaprag

Pharmacokinetics is the study of how the body interacts with substances over time, encompassing four key parameters: (1) *Administration/Absorption:* This describes how a drug is transported from the site of administration to systemic circulation; (2) *Distribution:* This parameter details how the drug disperses throughout the body; (3) *Metabolism:* This involves the biochemical transformation of the drug into various metabolites within the body; and (4) *Excretion:* This is the process by which the drug and its metabolites are eliminated from the body (Anker et al., 2018). Collectively known as ADME, these parameters are influenced by the substance's physiochemical and lipophilicity (Leeson et al., 2021; Kenny 2019). Variability in a patient's physiology can influence these processes, highlighting the importance of predicting and adjusting pharmacokinetic profiles to accommodate individual patient conditions. The pharmacokinetic profiles of the selected compounds are summarized in Table 3.

Table 3 Pharmacokinetics Profile of Selected Compound

Compound	Administration	Distribution	Metabolism					Excretion
	GI Absorption	BBB	CYP Substance					Pgp-Substrate
			CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4	
Asiaticoside	Low	No	Inactive	Inactive	Inactive	Inactive	Inactive	Yes
Dihydrocurcumin	High	No	Inactive	Active	Active	Inactive	Active	No
Procyanidin B1	Low	No	inactive	inactive	inactive	inactive	inactive	No
Procyanidin B2	Low	No	inactive	inactive	inactive	inactive	inactive	No
Gambogic acid	Low	No	inactive	inactive	inactive	inactive	inactive	Yes
Azelaprag	Low	No	inactive	inactive	inactive	inactive	inactive	Yes

In terms of administration, most of the compounds show low gastrointestinal absorption. Dihydrocurcumin is the exception, as indicated by the bioavailability radar. Additionally, the penetration of these compounds across the blood-brain barrier (BBB) penetration of each compound is minimal, suggesting that they are less likely to cause central nervous system (CNS)-related side effects. Regarding metabolism, only Dihydrocurcumin is predicted to be a substrate for cytochrome P450 (CYP) isozymes CYP2C19, CYP2C9, and CYP3A4. This is important for assessing potential drug interactions because CYP enzymes are crucial in drug metabolism and can be either induced or inhibited, affecting drug efficacy and safety. Clinical implications related to CYP are mostly concerned with the potential specific accumulation of certain drugs that are prescribed simultaneously. For distribution, Asiaticoside, Gambogic acid, and Azelaprag are predicted to be substrates for P-glycoprotein (P-gp). This transporter, which is found in various tissues, acts as a "housekeeping" protein, influencing the distribution and excretion of drugs. Compounds that are substrates for P-gp are generally excreted more effectively through the liver and kidneys (Anker et al., 2018). When it comes to safety, the profile of each compound is critical for drug development to minimize patient risk and identify compounds with a larger toxicity window. Gambogic acid is associated with high acute toxicity, having a predicted lethal dose for 50% of the population (LD_{50}) 500 mg/kgBW, compared to Azelaprag's 1000 mg/kgBW. Asiaticoside has the highest predicted LD_{50} at 4000 mg/kg BW. Despite its higher acute toxicity,

Gambogic acid is predicted to be inactive in terms of hepatotoxicity, cardiotoxicity, nephrotoxicity, mutagenicity, and carcinogenicity. This contrasts with other compounds that may have at least one potential toxicity, as detailed in Table 4. Determining and validating the effective dosage of these compounds in preclinical studies is essential before proceeding to clinical trials. Even with higher toxicity predictions, strategies such as chemical modifications or advanced drug delivery systems, such as liposomal formulations, may be utilized to mitigate toxicity and enhance safety (Liu et al., 2022).

Table 4 Toxicities Prediction of Top Five Compounds

Compound	Toxicity					
	Hepatotoxic	Cardiotoxic	Nephrotoxicity	Mutagenicity	Carcinogenicity	LD_{50} (mg/kgbw)
Asiaticoside	Inactive	Active	Active	Inactive	Inactive	4000
Dihydrocurcumin	Inactive	Active	Active	Inactive	Inactive	2000
Procyanidin B1	Inactive	Inactive	Active	Inactive	Inactive	2500
Procyanidin B2	Inactive	Inactive	Active	Inactive	Inactive	2500
Gambogic acid	Inactive	Inactive	Inactive	Inactive	Inactive	500
Azelaprag	Active	Inactive	inactive	Inactive	Active	1000

3.5. Future Directions and Study Limitations

This study focuses on the computational aspects of drug discovery, particularly in screening bioactive compounds found in Indonesian medicinal herbs. Even though this is not the first in-silico study finding apelin receptor agonists, to our knowledge, this is the first study that discusses the potency of Indonesia Medicinal Herbs bioactive compounds through in-silico combining docking and molecular fingerprint methods. Despite these facts, several strengths and limitations should be acknowledged, which are summarized in table 5.

The study pointed out several strengths. First, it leverages advanced *in-silico* methods to identify potential APR agonists from a diverse set of bioactive compounds found in Indonesian medicinal herbs. Second, the pharmacokinetic and safety profiles of the identified compounds were assessed using web-based tools, providing valuable insights into their therapeutic potential. Third, the use of multiple computational tools approach, including molecular docking to predict its binding activity and bioactivity prediction, enhances the robustness of these research findings.

However, this study has some limitations. Despite this study's internal validation methods for docking only using RMSD of redocking methods, we did not perform another validation metric such as Molecular Mechanics with Generalized Born and surface area solvation (MM/GBSA) that might be helpful for further validation results. We did this because our research group has proven that MVD has good external validation results (Tedjo et al., 2024), which has been compared with other docking tools and has been routinely used in our previous research (Dwira et al., 2024). Furthermore, our bioactivity prediction using molecular fingerprints does not aim to identify the activity cliff of selected isolated compounds from the plants (Dablander et al., 2023). Activity cliff is an important parameter in QSAR for determining the bioactivity of certain compounds based on molecular similarity that only differs in certain chemical chains. This study predicts the compound bioactivity based on SkelSpheres similarity, as published previously in our research (Heryanto et al., 2023). Lastly, while promising, these computational predictions rely on theoretical models and may not fully capture the complexities of *in-vivo* systems, for example, the role of biased ligands in apelin receptor agonists through hydrogen bonds in Tyr221 and Tyr309 (Portilla-Martinez et al., 2022).

Table 5 Strengths and Limitations of Recent Study.

Strength(s)	Limitation(s)
In-silico studies utilize combined molecular docking and molecular fingerprint (using machine learning) methods	Validated only using RMSD and redocking methods
High-throughput Identification of potential apelin receptor agonist of Indonesia medicinal plant bioactive compound	Not predicting the activity cliff of a certain compound
Implementing prediction of the pharmacokinetic profile of each compound	Not predicting biased agonist of apelin receptor
	Not validated using In-vitro or in-vivo systems

Aside from varied computational methods, future research should focus on validating study findings through experimental *in-vitro* studies—such as using primary cardiomyocytes treated with specific compound to induce hypertrophy, exploring potential drug interactions, and conducting in-vivo study—for instance, transaortic constriction rats, for heart failure modelling to address these limitations. This study identified gambogic acid, procyanidin B1, procyanidin B2, dihydrocurcumin, and asiaticoside as having favorable in-silico results. Based on these findings, further confirmation through in-vitro and in-vivo studies is essential to validate their binding

activity and pharmacokinetic profiles. These steps should be undertaken during preclinical studies before progressing to human trials.

4. Conclusions

This preliminary computational study identifies gambogic acid, procyanidin B2, dihydrocurcumin, procyanidin B1, and asiaticoside as promising drug candidates for development as apelin receptor agonists for heart failure therapy. Among these, Gambogic acid emerges as the most promising due to its favorable pharmacokinetics and safety profiles. As previously stated, preclinical confirmation is needed to validate the study results and further find optimized compounds to be tested in human studies. This might be planned by performing in-vitro studies, using primary cardiomyocytes or human-induced pluripotent stem-cells based technology, and in-vivo studies, aiming to investigate how pharmacokinetic and pharmacodynamic of lead compound works in different heart failure animal models since heart failure has puzzling complexity of phenotype and molecular features.

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Author Contributions

MRF and **WA** were concepting and designing the research; **MRF, WA, HW, SA, HW,** and **SWP** performed research methodology; **MRF, WA, MH, SA, HW, SWP,** and **NGK** performed data acquisition and analysis for research; **MRF, WA, HW, AT,** and **SWP** wrote the original manuscript draft; Entire authors were reviewed and edited for the final manuscript.

Conflict of Interest

The authors affirm no conflict of interest

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