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Study of Potential Antiobesity Compounds from Amylchlorogenate Derivatives on Leptin Hormone and Their Toxicity Using Molecular Docking Approach

Faridah Faridah[1*], Shirly Kumala[2], Gumilar Adhi Nugroho[2,4], Partomuan Simanjuntak[3].

[1]*Doctoral Program, Faculty of Pharmacy, Universitas Pancasila, South Jakarta, DKI Jakarta, Indonesia.*
[2]*Faculty of Pharmacy, Universitas Pancasila, South Jakarta, DKI Jakarta, Indonesia.*
[3]*National Research and Innovation Agency, Cibinong, Jawa Barat, Indonesia.*
[4]*Center for the Study of Natural Product for Degenerative Diseases, Faculty of Pharmacy, Universitas Pancasila, South Jakarta, DKI Jakarta, Indonesia*
*Corresponding Author: faridah@univpancasila.ac.id

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ABSTRACT: Chlorogenic acid, a type of phenolic acid, is a polar compound that has anti-obesity effects with unclear mechanisms. This study aims to obtain compounds that are active as antiobesity, their interaction with receptors and its toxicity. This research was carried out in several steps, internal validation of targets and methods using Yasara, docking of test compounds and positive control using PLANTs, interaction visualization using Pymol and toxicity testing using Protox-II. Validation results show four receptors and test method meet the requirements. Docking results of setmelanotide on receptor code 1PXH -113.81; 2QBP -109.163; 2QBR -110.113, 2; QBS -110.817 kcal/mol respectively. The docking results of the test compounds in 1PXH namely 7,4,5-Triamylchlorogenate (compound a) -114,333 kcal/mol. In 2QBP namely 7,3'-Diamylchlorogenate (110,152) (compound b), (compound a) (-109,818), 7,4,3',4'-Tetraamylchlorogenate (compound c) (-115,309), 7,5,3',4'-Tetraamylchlorogenate (compound d) (-112,85), 7,4,5,3',4'-Pentaamylchlorogenate (compound e) (-110,414) and 2',5'-Diamylchlorogenic acid (compound f) (-113, 565) kcal/mol. In 2QBR namely, (compound a) (-114,276), (compound e) (-111,059), and (compound f) (-110,398) kcal/mol. In 2QBS namely, (compound a) (-113.53), and (compound d) (-111,676) kcal / mol. The active site of amino acids that have affinity are, ARG45 and LYS120 in 1PXH; ASP48, SER118 and ARG47 in 2QBP; ASP48 and ARG24 in 2QBR; ASP48 and GLN262 in 2QBS code. Toxicity tests obtained oral LD50 of 5000 mg/kg BW (compounds a and f); 3800 mg/kg BW (compounds b, c, d and e). The potential compound that was active in all the test receptor codes was 7,4,5-Tripentylchlorogenate (compound a). All active test compounds were relatively safe.

KEYWORDS: antiobesity; chlorogenic acid; leptin hormone; toxicity; molecular docking.

1. INTRODUCTION

Over the last few decades, obesity has become an increasing public health problem worldwide, and its related conditions differ by region, for example, in China and Russia obesity is associated with hypertension, angina, diabetes and arthritis, whereas in India, it is associated with hypertension [1]. Obesity can also lead to a wide variety of other illnesses [2]. Overall, obesity is defined as the excessive accumulation or abnormal distribution of body fat, affecting health. It is classified, primarily, by body mass index (BMI, kg/m2), which is a very limited criterion. Obesity is complicated by other diseases such as type 2 diabetes mellitus, hepatic steatosis, cardiovascular diseases, stroke, dyslipidemia, hypertension, gallbladder problems, osteoarthritis, sleep apnea and other breathing problems and certain types of cancer (endometrial, breast, ovary, prostate, liver, gallbladder, kidney and colon), all of which can lead to an increased risk of mortality [3]. Cases related to pituitary, thyroid and adrenal gland diseases are considered an independent pathology but may indicate obesity [4].

The ideal anti-obesity drug would result in sustained weight loss with minimal side effects [5]. The mechanisms that regulate energy balance overlap with other physiological functions, and are influenced by social, hedonic and psychological factors that limit the effectiveness of pharmacological interventions [6]. Therefore, it is not surprising that anti-obesity drug discovery programs are filled with false starts, failures

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in clinical development, and drug discontinuation due to side effects that were not fully known at the time of launch [7]. Drugs that target pathways in metabolic tissues, such as adipocytes, liver and skeletal muscle, have shown potential in preclinical studies but none have yet reached clinical development. After its discovery in 1994, leptin became a great hope as an anti-obesity treatment target based on its ability to reduce food intake and increase energy expenditure [8]. However, treatment of obese people with exogenous leptin is unsuccessful in the majority of cases because most of them already have such high levels of leptin in circulation that they cannot respond anymore and defines a state called "leptin resistance". Leptin therapy is particularly effective in people with rare single gene mutations in the leptin gene [9].

Chlorogenic acid is a widespread natural compound with many important pharmacological effects, which is found in various plants [10]. It is also an important secondary metabolite in plants. In the form of plant extracts, in vitro and in vivo studies found that chlorogenic acid has pharmacological effects are antioxidant, anti-inflammatory, antibacterial, antiviral, hypoglycaemic, lipid-lowering, anti cardiovascular, antimutagenic, anticancer, immunomodulatory and others [11]. Therefore, it may play an important role in improving human health. For example, it may provide new ideas and new ways for the prevention and treatment of cardiovascular disease, cancer, diabetes and other chronic diseases, but the specific mechanism of action remains unclear [12].

Drug development and production is challenging because drug discovery is a time-consuming and resource-intensive process [13]. The process of drug discovery, lead optimization, drug design, and development has been accelerated by computers and information technology [14]. Due to its ability to reduce the time and resources required to discover new drugs, in-silico technology has emerged as an indispensable tool in the modern pharmaceutical industry. As a result of the development of computer algorithms and the accumulation of knowledge databases over time, computational prediction tools have recently been incorporated into every stage of the drug discovery process [15]. A computational method called "molecular docking" forecasts how well ligands will attach to receptor proteins. In recent years, molecular docking has emerged as a crucial component of in-silico drug development. This method involves speculating on how a tiny chemical and a protein would interact at the atomic level [16].

This study aims to obtain active anti obesity compounds from amylchlorogenate derivatives that act on the leptin hormone (the appetite suppressant) and determine its toxicity through molecular docking or *in silico* study.

2. MATERIALS AND METHODS

2.1. Material

This study used 30 compounds of amyl derivatives of chlorogenic acid. Target proteins with PDB codes 1PXH, 2QBP, 2QBR, 2QBS and 4I8N, setmelanotide as positive control. Hardware Laptop LENOVO-AV139ERJ Windows 11 Home Single Language 64bit (10.0, Build 22621), System Model: 82H7, IOS: GGCN49WW, Processor: 11th Gen Intel(R) Core(TM) 13-1115G4 @ 3.00GHz (4 CPUs), ~3.0GHz. The software used were Protein-ligand ANT system (PLANTS), YASARA, Chemsketch, ChemDraw, PyMOL, and R statistic.

2.2. Procedure of Docking Method Validation

Validation of the docking method is an internal validation by redocking the native ligand in each receptor using Yasara software. The validity was assessed based on the Root Mean Square Deviation (RMSD) value (<2A) where the value indicates the accuracy of the method to restore the native ligand position as similar as possible to the previous position. At first, the ligand and protein (receptor) preparations that will be used are carried out.

2.2.1. Protein preparation [14].

Proteins (receptors) in (.pdb) format were obtained from the Protein data bank (PDB) http://www.rcsb.org. Prepared with YASARA application made as Yasara object with file type .yob, then prepped protein.mol2, ref _ligand.mol2, ref_ligand.mol2 prepped on ChemSketsch to get 2D_mrv ligand, then performed 10 conformations saved as ligand.mol2. Then running docking using PLANTS Software until the best score is obtained, then checking the RMSD value in Yasara (requirement < 2 Å).

2.2.2. Ligand preparation [14]

Preparation of ligands (test compounds and positive controls) using Chemdraw, then prepared using ChemSketch at pH 7.4 saved as ligand_ 2D.mrv, then made 10 conformations saved as ligand and file format.mol2.

2.3. Docking Method Ligand against The Receptors

Docking was performed on ligands (test compounds and positive controls) with receptors (according to their respective PDB codes) using PLANTs software [17]. The docking score results of the test compound and positive control of each receptor code were inputted in the R statistical application to find the p-value, then analyzed whether it was eligible or not (p> 0.05). The statistical analysis results of this test, using the One-Sample T-test method, is used to compare data derived from one sample with a reference value. The conclusion in the T-test is based on the p-value. If the p value obtained > 0.05, it means that there is no significant difference between each variable of the test compound and the positive control so it is concluded that the compound is active. If the p-value obtained <0.05, it means that there is a significant difference between the variables of the test compound and the positive control so that it can be concluded that the compound is not active.

2.4. Visualization of Docking Results

Visualization of active test compounds with proteins (all .mol2 file types) was performed using Pymol software. Parameters analyzed include bond distance, bond type, and amino acid residues in the receptor that bind to the test compound [18].

2.5. Toxicity Test

Toxicity tests were conducted on active test compounds and positive controls (in the form of SMILE) using Protox-II (Prediction Of Toxicity Of Chemicals) software [19]. The observed assays include hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, cytotoxicity, androgen receptor (AR), aromatase, estrogen receptor alpha (ER) and PPAR-Gamma [20].

3. RESULTS

3.1. Docking Method Validation

The results of the receptor validation used are in Table 1. Of the 5 receptor codes used, there is 1 receptor that does not meet the requirements (RMSD>2A), namely 4I8N (RMSD = 4,0893), so for the next docking process only with 4 receptor codes, namely 1PXH, 2QBP, 2QBR and 2QBS.

Table 1. Method validation results on five leptin receptors

No	Protein	PDB Code	RMSD (Å)
1.	*Crystal structure of protein tyrosine phosphatase 1B with potent and selective bidentate inhibitor compound 2*	1PXH	1,4603
2.	*Crystal structure of ptp1b-inhibitor complex*	2QBP	1,2919
3.	*Crystal structure of ptp1b-inhibitor complex*	2QBR	1,4854
4.	*Crystal structure of ptp1b-inhibitor complex*	2QBS	1,1576
5.	*Crystal structure of protein tyrosine phosphatase 1b in complex with an inhibitor [(4-{(2s)-2-(1,3-benzoxazol-2yl)-2-[(4 fluorophenyl)sulfamoyl]ethyl}phenyl)amino](oxo)acetic acid*	4I8N	4,0893

3.2. Docking Ligand against The Receptors

The docking results of the positive control and test compound were carried out on receptors that met the requirements at the receptor validation stage, namely receptor codes 1PXH, 2QBP, 2QBR and 2QBS because they had RMSD (Root Mean Square Deviation) values ≤ than 2.0 Å (Figure 1). The positive control and test compounds are listed in Figure 2 until Figure 5. In receptor code 1PXH there is only one active test compound namely 7,4,5-Triamylchlorogenate, in receptor code 2QBP there are six active test compounds namely 7,3'-

Diamylchlorogenate; 7,4,5-Triamylchlorogenate; 7,4,3',4'-Tetraamylchlorogenate; 7,5,3',4'-Tetraamylchlorogenate; 7,4,5,3',4'-Pentaamylchlorogenate; 2',5'-diamylchlorogenic acid, in receptor code 2QBR there are three active test compounds namely 7,4,5,3'-Tetraamylchlorogenic; 7,5,3',4'-Tetraamylchlorogenic; 2',5'-diamylchlorogenic acid and in receptor code 2QBS there are only two active test compounds namely 7,4,5-Triamylchlorogenate and 7,4,3',4'-Tetraamylchlorogenate.

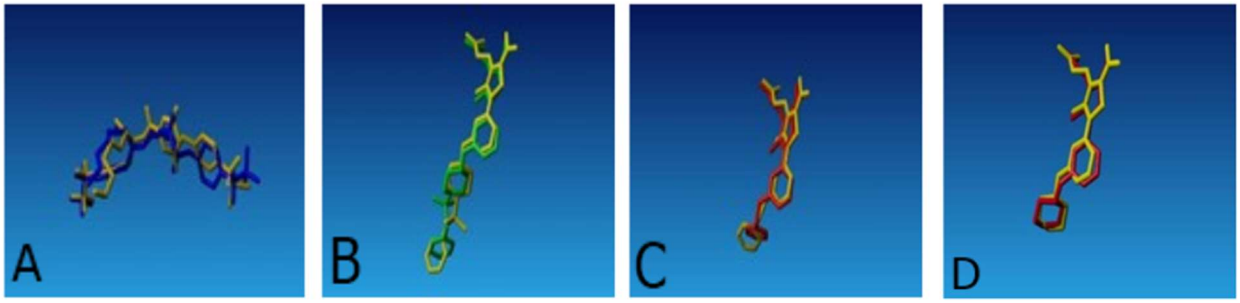

Figure 1. Validation results based on Superimposed native ligand with docking *pose on* 1PXH(A), 2QBP(B), 2QBR(C) and 2QBS(D)

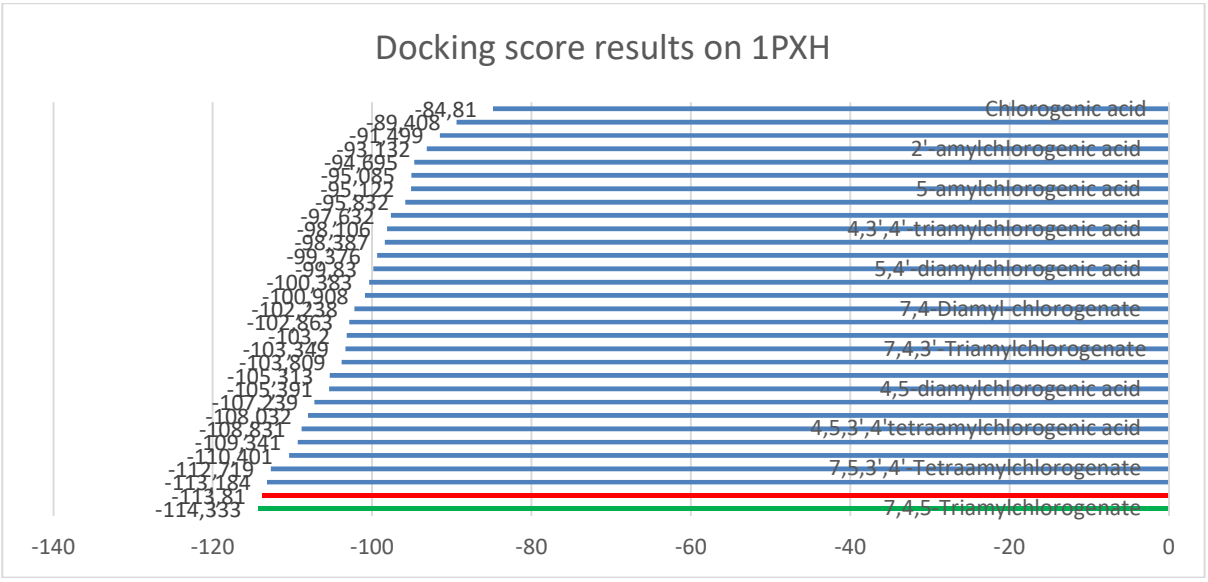

Figure 2. Docking score results on 1PXH; blue line indicates as inactive compound, red line indicate as positive control and green line indicate as the active compound

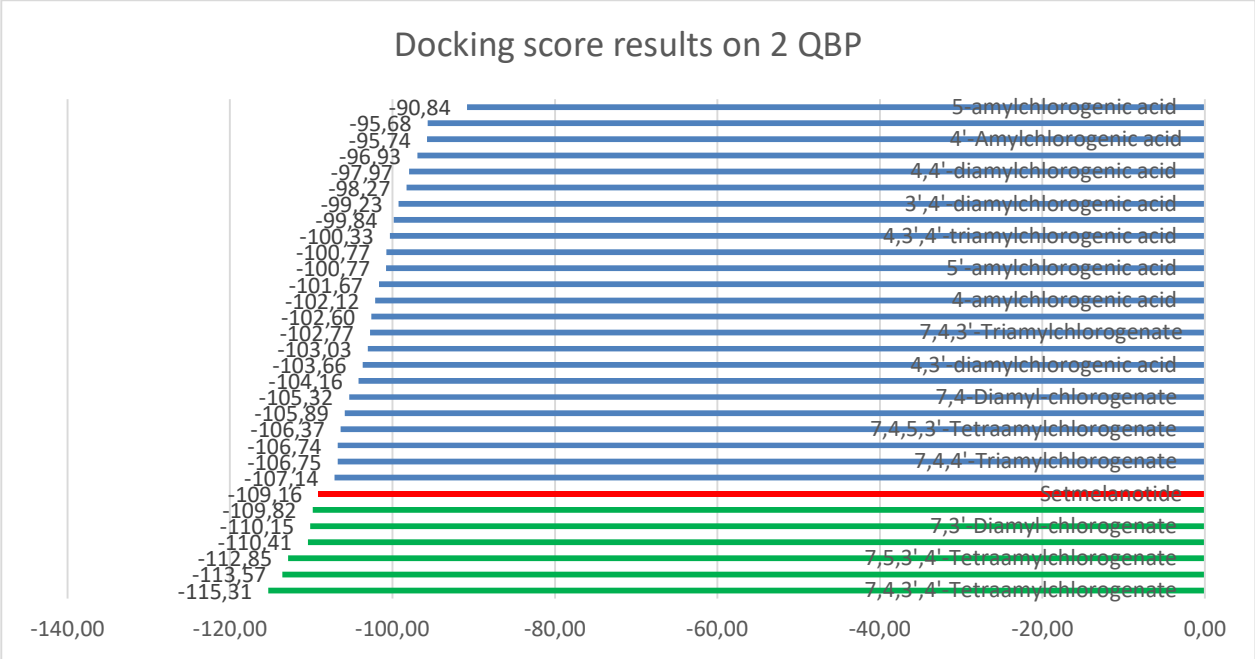

Figure 3. Docking score results on 2QBP; blue line indicates as inactive compound; red line indicate as positive control and green line indicates as the active compound

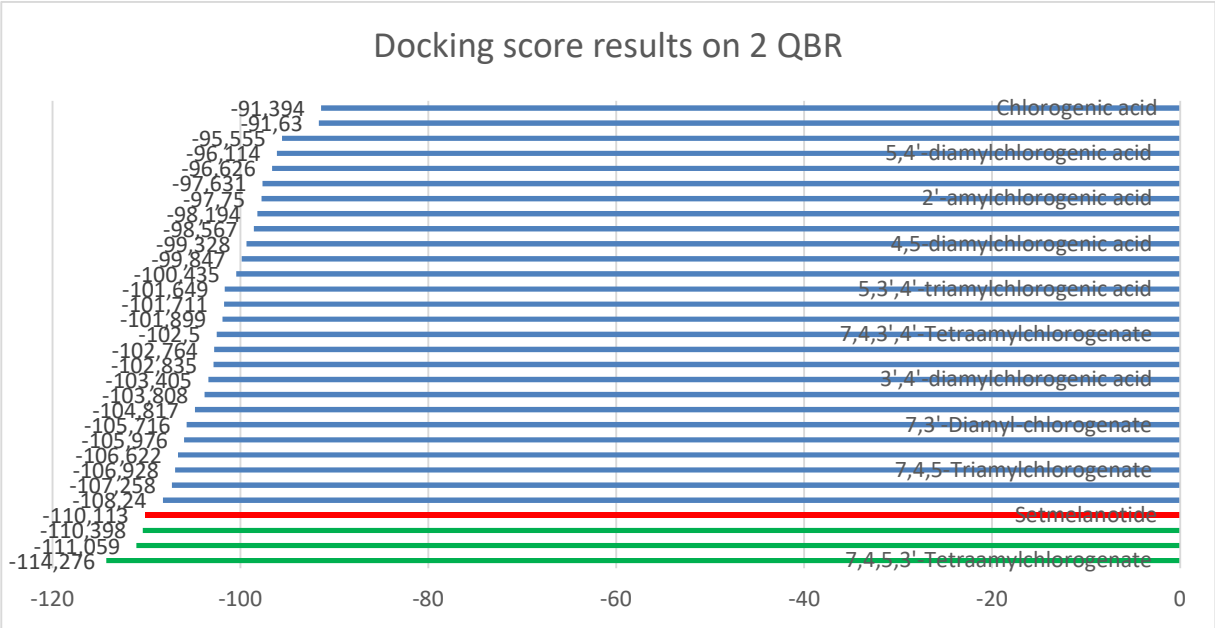

Figure 4. Docking score results on 2QBR**;** blue line indicates as inactive compound; red line indicate as positive control and green line indicates as the active compound

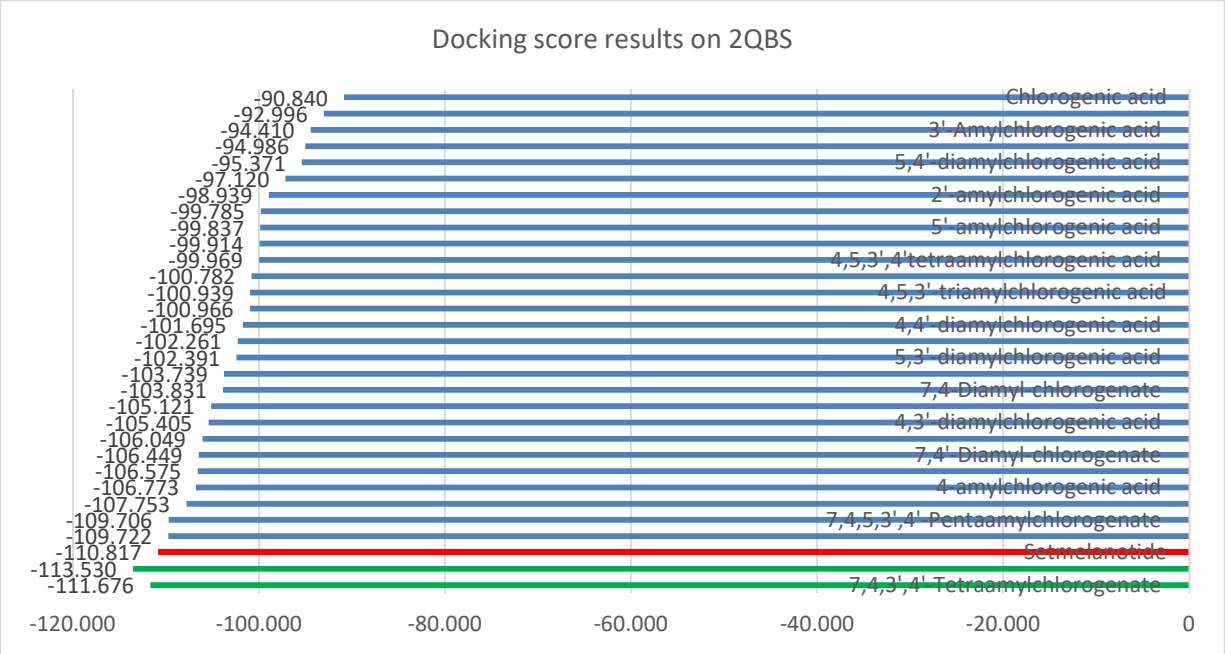

Figure 5. Docking score results on 2QBS; blue line indicates as inactive compound, red line indicate as positive control and green line indicates as the active compound

3.3. Visualization Of Docking Results

The results of the interaction between the test compounds with the leptin receptor binding pocket with the code 1PXH, 2QBP, 2QBR and 2QBS can be found in the Table 2 to .5 and Figure 6 to 9 respectively. Visualization of compounds in the binding pocket is described in three dimensions (3D) using Pymol software, the visualization results can be used to determine the bonding distance between active compounds and receptors, type of bond and interacting groups [18].

Table 2. Interaction of test compounds with leptin receptor code 1PXH

No	Test Compound	Bond Type	Group that Bonds		Bond distance(Å)
			Test Compound Group	Protein Group	
1	7,4,5-Triamylchlorogenate	Hydrogen Bonding	3': -C-O-**H** 7 : -C=**O** 9':**-** C=**O**	C=**O** (ARG45) **H**-N-H-H (LYS116) **H**-N-H-H(LYS120)	1,8 2,0 2,0

Table 3. Interaction of test compounds with leptin receptor code 2QBP

No	Test Compound	Bond Type	Group that Bonds		Bond distance (Å)
			Test Compound Group	Protein Group	
1	7,3′-Diamylchlorogenate	Hydrogen Bonding	7 : -C=**O** 4 :-C-O-**H** 5 : -C-O-**H** 4′ : -C-O-**H**	**H**-N(ARG254) C=**O** (ASP48) C=**O** (ASP48) C-**O**-H (TYR46	2,3 1,8 2,1 2,0
2	7,4,5-Triamylchlorogenate	Hydrogen Bonding	7 :-C=**O** 7 : -C-**O**-C	C-O-**H** (SER118) C-O-**H** (TYR46)	2,6 2,5
3	7,4,3′,4′-Tetramylchlorogenate	Hydrogen Bonding	9′: **-** C=**O** 9′: **-** C=**O**	N-**H** (ARG47) N-**H**(ASP48)	2,7 2,0
4	7,5,3′,4′-Tetramylchlorogenate	Hydrogen Bonding	7 : -C=**O** 4 : C-O-**H**	**H**-N-H (ARG254) C=**O** (ASP48)	2,1 2,0
5	7,4,5,3′,4′-Tetramylchlorogenate	Hydrogen Bonding	4′ : -C-**O**-C 4 : -C-**O**-C 5 : -C-**O**-C	**H**-N-H- H(LYS120) N-**H**(ARG47) (2,1Å) N-**H**(ARG47) (2,4Å)	2,4 2,1 2,4
6	2,5-Diamylchlorogenic acid	Hydrogen Bonding	7 : -C=**O** 4′ : -C-O-**H** 4 : -C-O-**H** 5 : -C-O-**H**	**H**-N-H(ARG254) O-H (TYR46) C=**O**(ASP48)(1,8Å) C=**O**(ASP48)(2,1Å)	2,1 2,0 1,8 2,1

Table 4. Interaction of test compounds with leptin receptor code 2QBR

No	Test Compound	Bond Type	Group that Bonds		Bond distance(Å)
			Test Compound Group	Protein Group	
1	7,4,5,3′-Triamylchlorogenate	Hydrogen Bonding	3′: -C-O-**H** 7 : -C=**O** 9′:**-** C=**O**	C=**O** (ARG45) **H**-N-H-H LYS116) **H**-N-H-H(LYS120)	1,8 2,0 2,0
2	7,5,3′,4′-Triamylchlorogenate	Hydrogen Bonding	1 : C-O-**H** 3′: -C **O**-H 5: C-**O**-C 4 : -C-O-**H** 5: -C-**O**-C	C=**O**(ASP48) **H**-N-H- H(LYS120) N-**H**(ARG24) C=**O**(GLN262) **H**-N-H(GLN262)	1,6 2,2 2,8 2,0 1,7
3	2,5-Diamylchlorogenic acid	Hydrogen Bonding	4 : -C-O-**H** 3 : -C-**O**-C 7 : -C=**O** 7 : -C=**O** 7 :-C=**O**	C=**O**(ASP48) **H**-N-H(GLN262) N-**H**(ARG24) **H**-NH(ARG254) **H**-NH(ARG254)	2,3 2,6 2,1 1,9 2,1

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Table 5. Interaction of test compounds with leptin receptor code 2QBS

No	Test Compound	Bond Type	Group that Bonds		Bond distance(Å)
			Test Compound Group	Protein Group	
1	7,4,5-Tetraamylchlorogenate	Hydrogen Bonding	1 : -C-O-**H** 3′ : -C O-**H**	C=**O**(ASP48) C=**O**(ARG45)	2,1 1,6
2.	7,4,3′,4′-Tetraamylchlorogenate	Hydrogen Bonding	3′ : -C **O**-C 1 : -C-O-**H** 4 : -C-**O**-C 5 : -C-O-**H**	**H**-N-H-H(LYS120) C=**O**(ASP48) N-**H**(GLN262 C=**O**(GLN262)	2,2 2,1 2,1 2,0

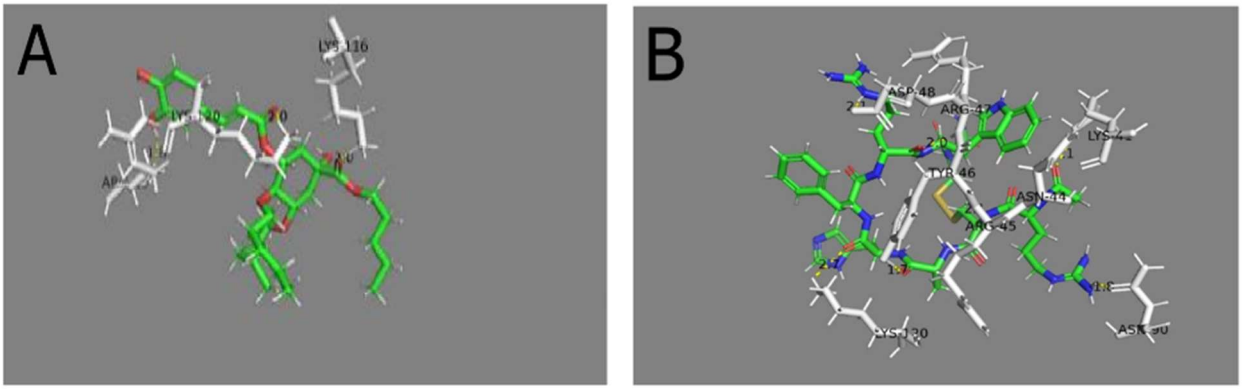

Figure 6. Visualization of test ligand a .7,4,5-Triamylchlorogenat and b. positive control setmelanotide on 1PXH

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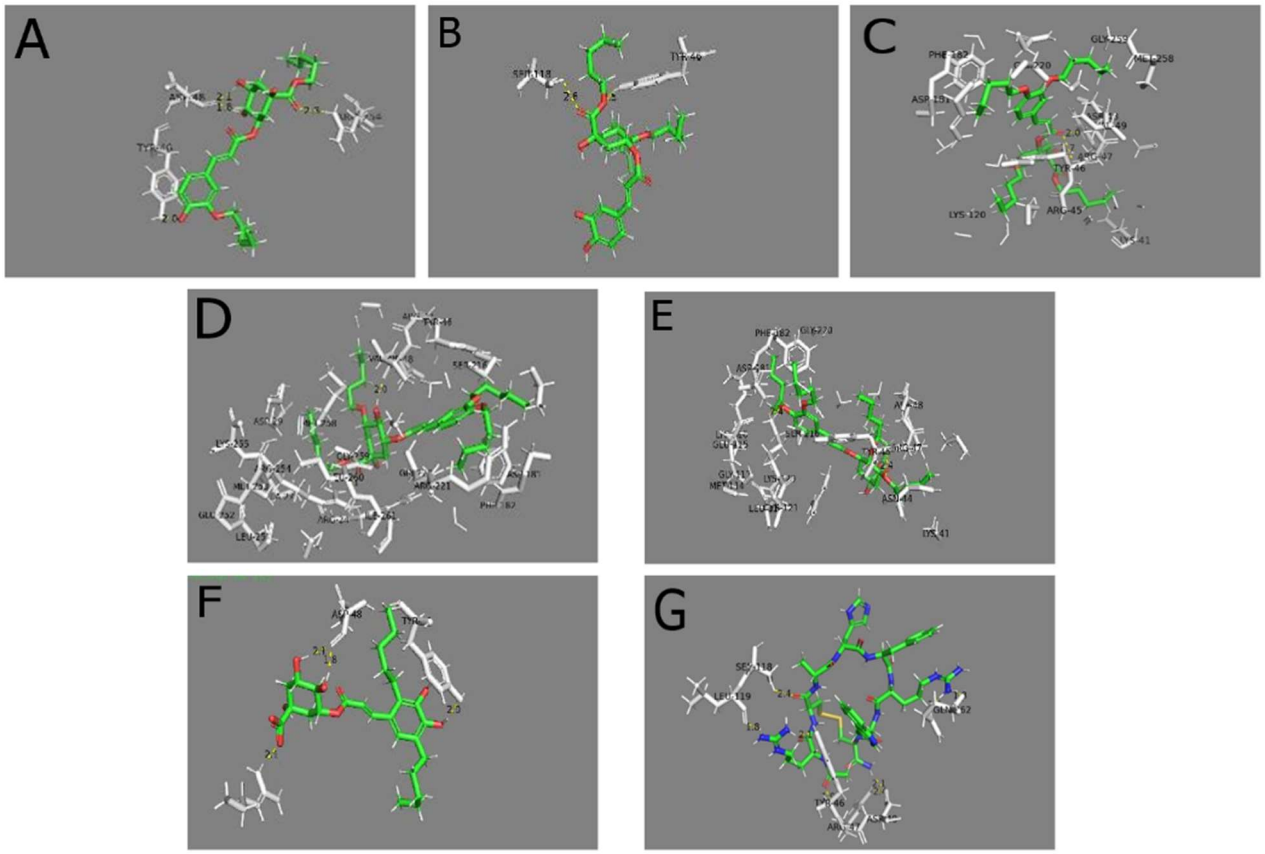

Figure 7. Visualization of test ligand A. 7,3'-Diamylchlorogenate B. 7,4,3',4'-Tetraamylchlorogenate C. 7,4,5 -Triamylchlorogenate D. 7,5,3',4'-Tetraamylchlorogenate E. 7,4,5,3',4'-Pentaamylchlorogenate F. 2'-5'-diamylchlorogenic acid and G. Setmelanotide (positive control) on 2QBP

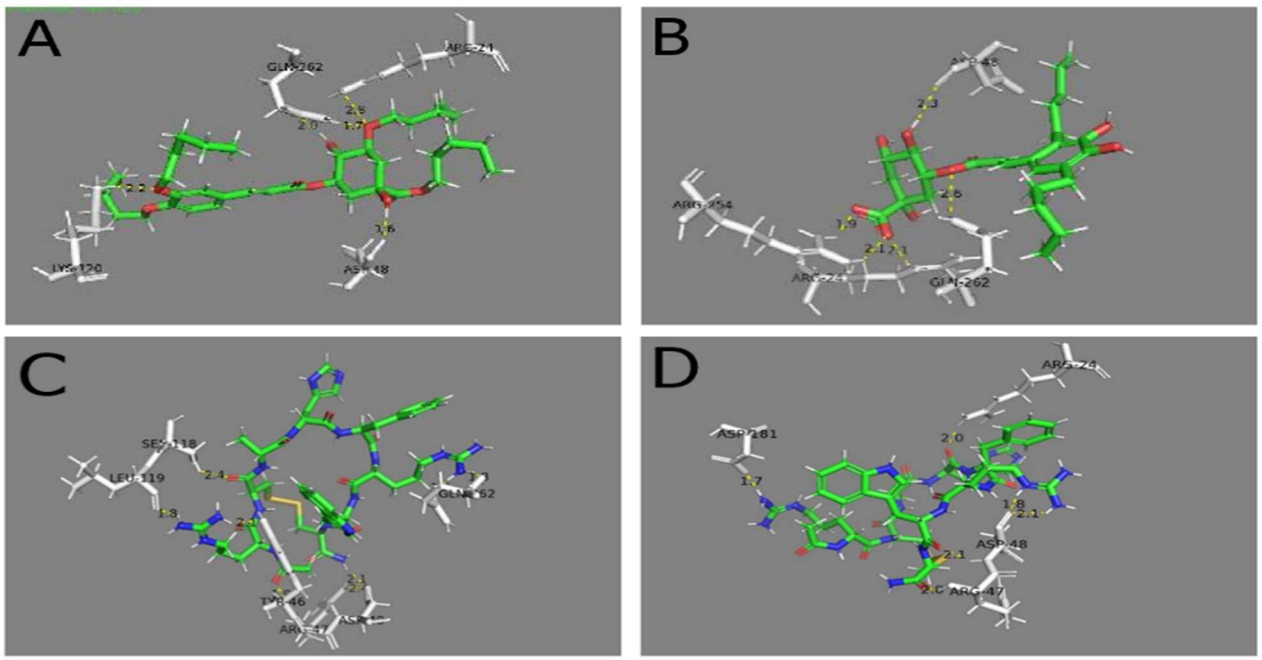

Figure 8. Visualization of test ligand A. 7,5,3',4'-Tetraamylchlorogenate; B. 2'-5'-diamylchlorogenic acid; C. 7,4,5-Triamylchlorogenat and positive control D. setmelanotide on 2QBR

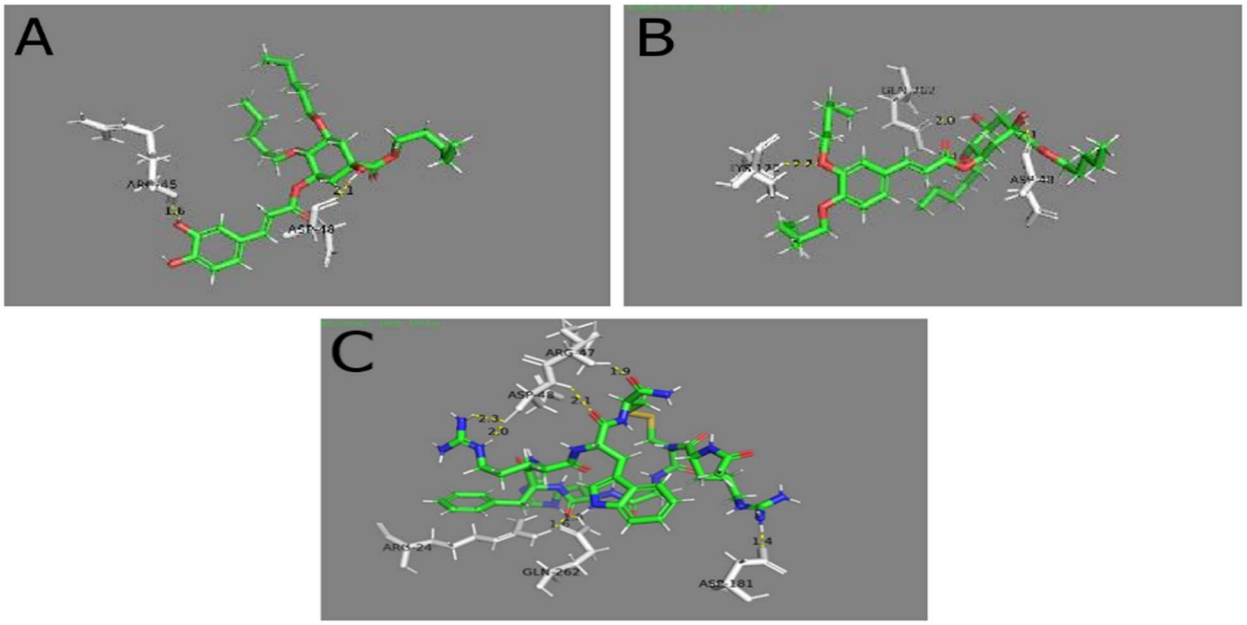

Figure 9. Visualization of test ligand A. 7,4,5-Triamylchlorogenate; B. 7,4,3',4'-diamylchlorogenate and positive control C. setmelanotide on 2QBS

3.4. Toxicity Test

Toxicity tests on 6 active compounds showed toxic results on Immunotoxicity can be found in Figure 10.

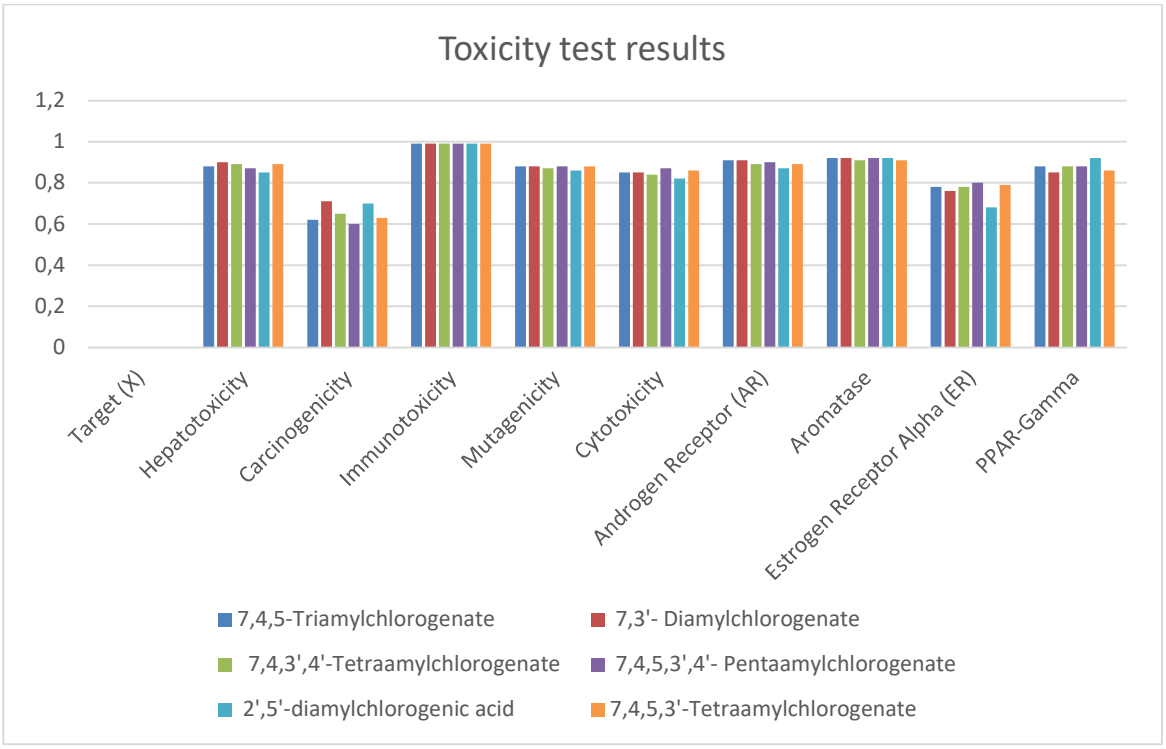

Figure 10. Toxicity test Result of active compounds

4. DISCUSSION

The receptors selected in this study are receptors with codes 1PXH, 2QBP, 2QBR, 2QBS, and 4I8N. The basis for selecting these receptors is that the receptors are crystal structures of leptin receptors that play a role in obesity [21]. This is because if using a non-crystalline structure, it will usually have problems with validation because in this experiment the validation used is internal validation, while non-crystalline structures are usually validated by external validation. The source organism of the receptor comes from homo sapiens (human), so its shape has been adapted to the original structure of the receptor in the human body, there is no mutation in the amino acids that make up the receptor, so there is no bonding disorder when doing the docking process with the test compound (ligand). The main requirement in validating the docking method is the RMSD (Root Mean Square Deviation) value of less than 2.0 Å. This is a measure to assess the ability of the method in terms of its accuracy. The smaller the RMSD value, the better the predicted ligand position because it is closer to the original conformation [22].

One drug that has activity as an antiobesity at the leptin receptor is setmelanotide and is used as a positive control [7]. The positive control compound aims as a comparison in measuring the ability of a test compound that works on the target receptor. Good activation ability is seen from the low or negative docking score. The lower the score the stronger the affinity so that the docking simulation will provide high stability. This study used 30 amyl derivative compounds of chlorogenic acid starting from mono to penta amyl substitution variations based on their ability to activate leptin receptors by molecular docking method. *In-silico* molecular docking is one of the bioinformatics methods that could be used for visualizing and discovering the actions of unknown chemical or metabolites compounds by identification of their molecular targets using chemo informatics and bioinformatics connected with the biological system, analyzing the orientation of single molecule to another when bound to each other to form a stable complex, predicting the drug molecules which could bind to a specific target known to be involved in causing a disease, and frequently used to determine the binding affinity of small molecule to their protein targets.

In-silico molecular docking methods in drug discovery are consist of four steps generally: protein preparation, ligand preparation, molecular docking study (validation of molecular docking methods, analysis of molecular docking with computational software, analysis of molecular docking result and structure visualization) and toxicity prediction. Based on the docking results of 30 test compounds and positive controls in Figures 2-5, there is an opportunity to obtain six potential compounds as antiobesity candidates with clear mechanisms as activators of the hormone leptin (appetite suppressant). Chlorogenic acid is a quinic acid conjugate of caffeic acid. It is an ester formed between caffeic acid and the 3-hydroxyl of L-quinic acid. This polyphenol is naturally present in substantial amounts in the green coffee beans, and is reported to be beneficial in hypertension, hyperglycemia, antimicrobial, antitumor, memory enhancer, weight management etc. Further, it is also reported to have anticancer, antioxidant and anti-inflammatory activities. Since the last decade, CGA drew public attention for its widely recommended use as a medicine or natural food additive supplement. By modifying its structure with amyl derivatives, compounds with lower polar properties are obtained and there are derivatives that are more active than chlorogenic acid. Figures 6 - 9 show the visualization of the interaction of

the test compound with the receptor. The more interaction (bonding) between the test compound and the receptor and the closer the bonding distance, the more active the test compound is. The docking results show that there are six derivatives that are more active than the positive control (setmelanotide) and have the potential to be synthesized.

To achieve sensitive and specific mechanism-based prediction of drug toxicity, the tools of systems pharmacology will be integrated using structured ontological approaches, analytics, mathematics, and statistics. Success of this effort is based on the assumption that a systems network that consists of drug-induced perturbations of physiological functions can be characterized. Mechanism-based prediction and evaluation of drug toxicity constitute an evolving science whose development is critical to drug discovery, development, and regulatory evaluation and whose goal is to make advances in human therapeutics available while protecting public health [23]. Attaining this objective requires new approaches in integrative pharmacology that have only recently become available. The interaction between toxicity and potency is crucial for effective drugs. Figure 10 shows the toxicity test results of the six active compounds. This is done to ensure that the active compounds are not toxic or relatively safe so that they are feasible to synthesize. The active compounds obtained showed immunotoxic properties. Immunotoxicity is defined as adverse effects on the functioning of both local and systemic immune systems that result from exposure to toxic substances including chemical warfare agents. The impact of immunotoxicity is known to be altered immune function and increased sensitivity to infection following exposure to environmental chemicals and therapeutic drugs, so other modifications must still be made to obtain a safer drug candidate.

5. CONCLUSION

The results showed that there was one test compound that was active on all test receptors, is 7,4,5-Tripentyl-chlorogenic. All active test compounds were relatively safe.

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Conflict of interest statement: The authors declare no conflict of interest.

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