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IN-SILICO STUDY OF *Manotes asiatica* AS CANDIDATE FOR ANTIOBESITY

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ABSTRACT

It is believe that *Manotes asiatica* could be used for obesity beside other medicinal uses including an aphrodisiac, as well as the relief of fever, intestinal worms, dysentery, diarrhea, indigestion, and jaundice. Obesity is is the one of serious health problem around the worlds. World Health Organization reported that more than three hundred billion of adult was obese. Orlistat, a patent drug which used to overcome this disease is a synthetic drug. Natural compounds of plant such as *M. asiatica* can be used to treat obesity. The aimed of this study use molecular docking to screening antiobesity drug candidates from *M. asiatica* such as eurycomalactone, eurycomanol, longilactone, laurycolactone, , and quassinoid. Docking was done towards interaction between FTO reseptor and compound of *M. asiatica* as ligand tests. Orlistat was used as control ligand. Docking, Lipinksi's rule of five and pre-Admet results showed that Eurycomalactone have a potential to be antiobesity drug.

Keywords : *Manotes asiatica*, in silico, antiobesity, FTO

INTRODUCTION

Manotes asiatica, commonly called longjack is a flowering plant in the family Simaroubaceae. It is native to Indochina (Cambodia, Laos, Malaysia, Myanmar, Thailand and Vietnam) and Indonesia (the islands of Borneo and Sumatra), but has also been found in the Philippines. This plant originates from southeast asia and is known as traditional herbal medicine that is used to threat various diseases. Active compounds that have pharmacological and biological effects are found in the roots, bark, leaves and stems of this plant. Some bioactive compounds contained in *M. asiatica* are sent quassinoids, alcaloids, triterpenes, steroid, biphenyl neolignan, eurylactone, laurycolactone, eurycomalactone and squalene derivatives. Quassinoids is the most bioactive group in the root of *M.asiatica* (Rehman, 2016). According to research conducted by Lahrita et al in 2015 showed that extracts from the root of *M.asiatica* can be collected by lipids in adipose tissue without any side effects (Lahrita, 2015).

Obesity is still a serious problem in the world of health. The world health organization (WHO) report that there are more than one billion adults who had overweight and three hundred billion suffered obesity clinically (Cao, 2010). Obesity should be considered if the value of the body mass index reach has more than 30 kg/m^2 (Frayling, 2007). Obesity can be caused by several factors which involve the consumption of high calory foods such as sugar and fatty foods, lack of physical activity, and genetics (NHS, 2019). Obesity is major cause of death due to behaviour with other emerging disease such as diabetes, hypertention, stroke, metabolic disorders, as well as heart disease and some cancers (Frayling, 2007). Obesity therapy requires 30% more cost than non obesity, so other therapy is needed to overcome disease as well as minimal cost therapy (Lucy, 2018).

This study will be determine several bioactive compounds contained in *M. asiatica* plants such as eurycomalactone, eurycomanol, laurycolactone, longilactone, FTO reseptor and screening compound for anti-obesity drugs.

MATERIALS AND METHOD

Materials

The materials used in this research are 3D protein complex of FTO/ Fat Mass and Obesity-Associated (code 4IE5) obtained from Protein Data Bank (www.rscb.org), 3D structure of test ligands (eurycomalactone, eurycomanol, laurycolactone, longilactone, quassinoid) and control ligand (orlistat) were obtained from the PubChem database, Autodock Tools 4.0.1 program, Discovery Studio Visualizer 3.5, ChemDraw Ultra 12.

Method

FTO reseptor and ligands needeed for this research are pre-prepared by the addition of charges and hydrogens atom use Discovery Studio program and save in pdbqt format. Validation is done by redocking the native ligand to the FTO reseptor in Autodock Tools 4.0.1 and its parameter are recorded for use in the docking process of test and control ligands. Docking was performed on seven test ligands and one control ligand with the following parameters : coordinate setting are x = 31.483, y = -7.422, z = -23.142; box size x,y,z = 40; running for 100 times. The resulting docking output are the form of free bond energy (ΔG) and the constanta of inhibition (Ki).

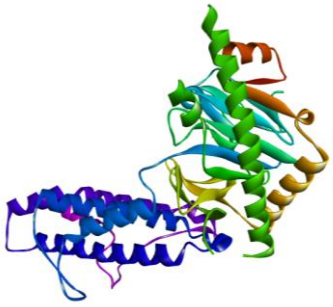
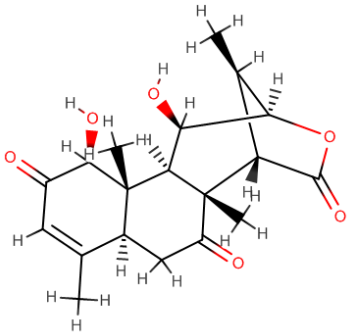


Figure 1: 3D structure of FTO protein with code 4IE5 (www.rscb.org)

Eurycomalactone



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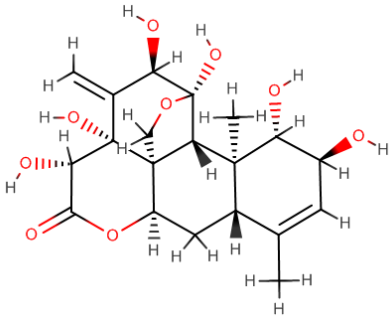
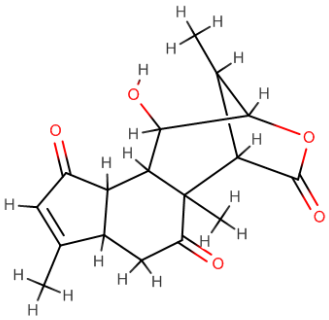
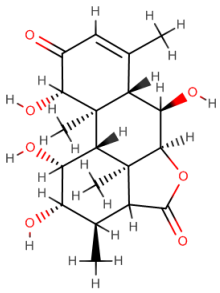


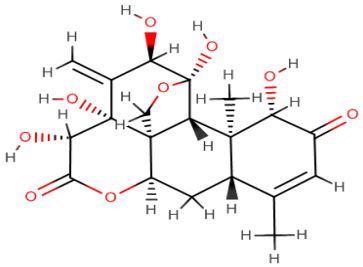
Laurycolactone



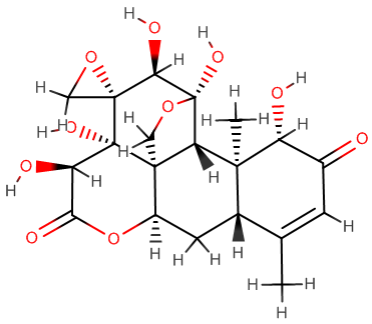
Longilactone



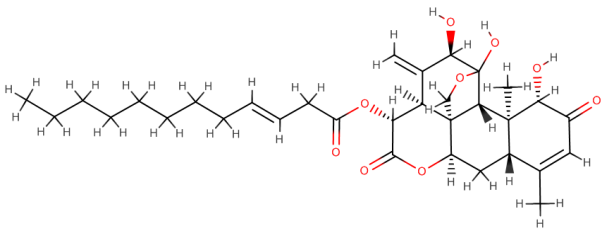
Pasakbumin A



Pasakbumin B



Quassinoid



Orlistat

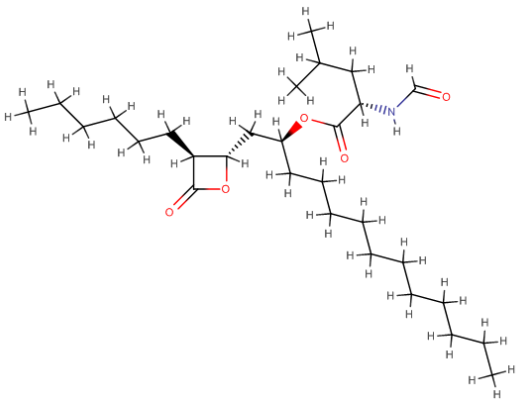


Figure 2: 2D structure of ligands in this study

RESULT AND DISCUSSION

Before carrying out the process of docking the test molecules from the *M.asiatica* plant, validation is done first on the native ligand that binds to the FTO reseptor namely N-[3-hydroxypyridin-2-yl)carbonyl]glycine (MD6) to determine whether the reseptor can be used or not. The reseptor downloaded at the protein data bank website can be used during the docking process in the RMSD value generated from the redocking process is under 2 Å. The RMSD value generated from the redocking process of native MD6 ligand with 4IE5 reseptor is 1.570 Å. This result shows that the 4IE5 reseptor can be used during the docking process of control and test ligands.

Molecular docking process was carried out on seven test ligands and one control ligand using the same active side as during the validation process. Molecular docking results can be seen in Table 1.

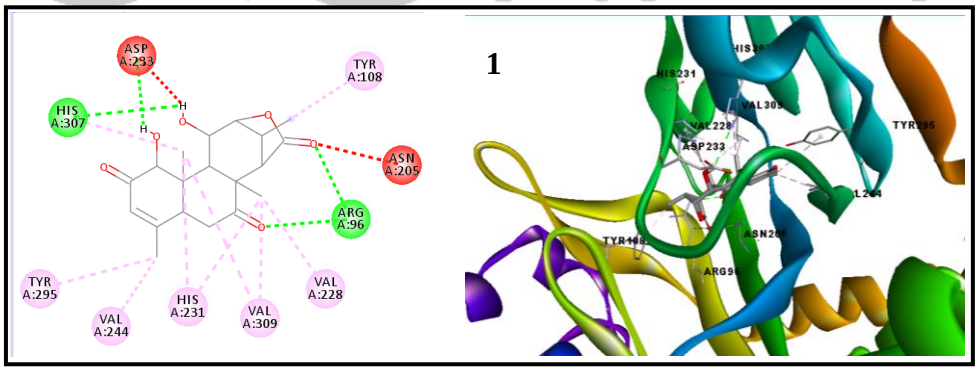
Table 1: Interaction test and control ligands to amino acid residues in FTO (4IE5)

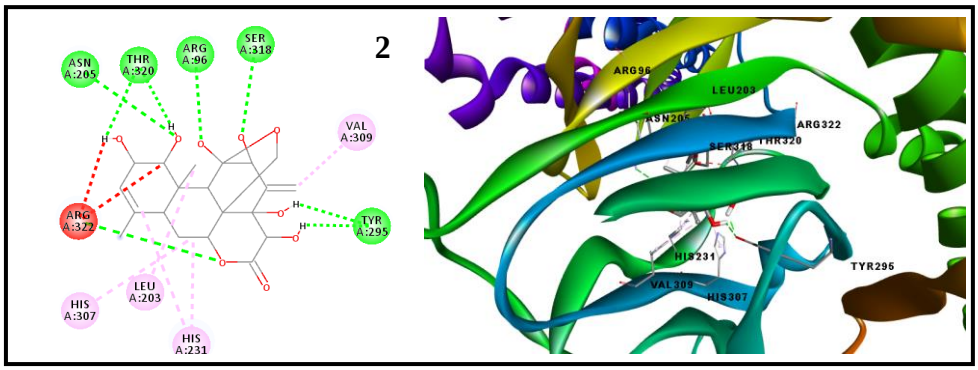
Ligands	Hydrogen bonds with amino acid residues	ΔG (kcal/mol)	Ki (mM)
Eurycomalactone	HIS307, ARG96	-4.29	0.717
Eurycomanol	ASN205, THR320, ARG96, SER318,TYR295	-0.06	896.81
Laurycolactone	ARG316, SER318, ASN205, ARG96	-4.93	0.243
Longilactone	ARG96, ARG316	+0.10	-
Pasakbumin A	THR320, ASN205, ARG96, SER318, TYR295	-0.20	717.28
Pasakbumin B	ARG96, ASN205, TYR106, GLU234	+2.61	-
Quassinoid	GLU234, TYR106	-2.93	7.13
Orlistat (kontrol)	SER318, ASN205	-2.54	13.82

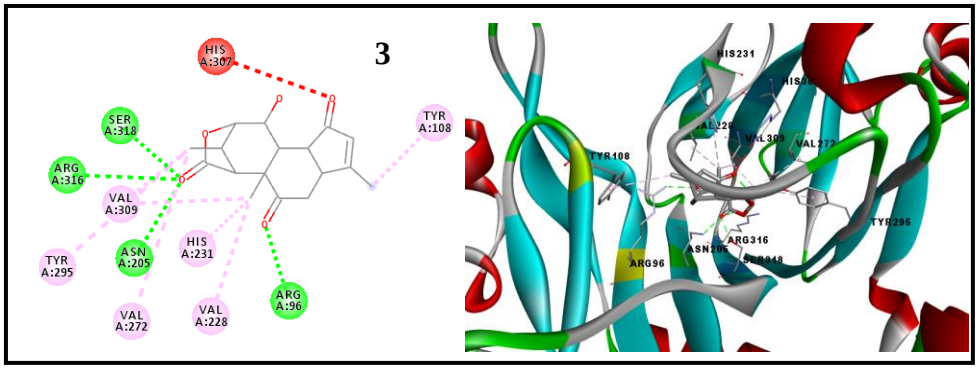
The interaction result of the test and control ligands of the FTO protein produced data in the form of bond types, interaction with amino acids residues, Gibbs free energy value (ΔG), and constanta of inhibition value (Ki). Native ligand MD6 form hydrogen bonds with five amino acids residues including SER318, ARG316, TYR295, ASN205, dan THR320. Control ligand (orlistat) form hygrogen bonds with two amino acid residues, SER318 dan ASN205. The number of amino acid residues of hydrogen bonds that bind to native MD6 ligands is greater than that of control ligands, this is because MD6 is a related ligand that contains inhibitors that can be used in FTO reseptor (Aik et al, 2013). Hydrogen bonds with activated amino acid residues are only SER318 and ASN205. Both of these amino acids are available in native ligands and conrol ligand and have a important role in stable bonds. In addition to the two amino acids, the amino acid ARG96 also plays a role. This can be seen from the results of docking on all test relationships that show hydrogen bonds with these amino acids. Of the seven test compounds, eurycomalavtone compound doesn not have hydrogen bonds with the same amino acid as

native ligand but binds hydrogen with ARG96. Eurycomanol has hydrogen bonds with amino acid residues similar to native ligand namely ASN205, SER318, TYR295, dan THR320. Laurycolactone compound has a hydrogen bonds with amino acid residues that are the same as native ligand, ARG316, SER318, and ASN205. Longilactone compound has hydrogen bonds with amino acid residues similar to native ligands, namely ARG316. Pasakbumin A compound has hydrogen bonds with amino acid residues similar to native ligand, THR320, ASN205, SER318, and TYR295. Pasakbumin B has hydrogen bonds with same amino acid residues as the native ligand, ASN205. Longilactone does not has hydrogen bonds with amino acids same as native ligand, but contain hydrogen bonds with ARG96. Quassinoid compounds do not have hydrogen bonds with the same amino acid as native ligand. Interaction of ligands with amino acid residues can be seen in Table 1.

Gibbs free energy value (ΔG) show the stability value of the bond between the reseptor and the ligan. The smaller (negative) value of free energy, the better level of stability of the bond and results in a strong bond. Based on the result of the docking that has been done, its known that the compound that have a smaller ΔG value compared to orlistat control drugs are eurycomalactone, laurycolactone, and quassinoid. All three ligands have a more stable and stronger bond when compared to orlistat control ligands to FTO reseptor. This is also in line with the value of the inhibition constanta. The smaller value of inhibition constanta, it is better to be used as a drug candidate. All three compounds showed smaller Ki values when compared to control drugs. The result can be seen in Table 1.






3
HIS A:307
SER A:318
ARG A:316
VAL A:309
TYR A:295
ASN A:205
HIS A:231
VAL A:272
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HIS231
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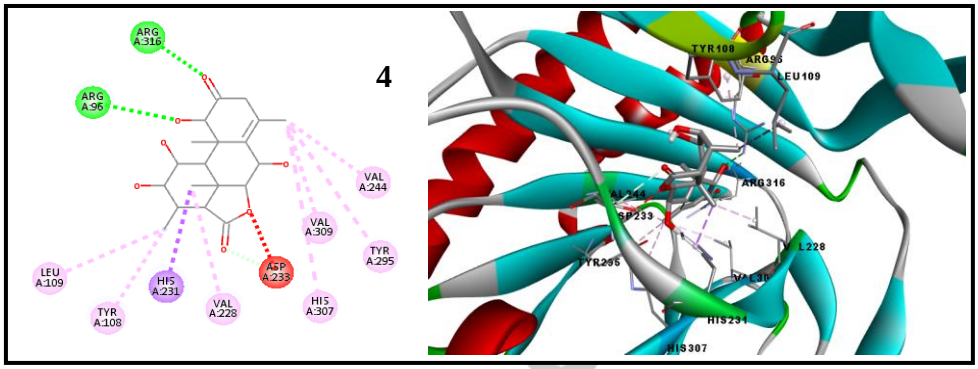
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ARG A:96
VAL A:244
VAL A:309
TYR A:295
LEU A:109
HIS A:231
ASP A:233
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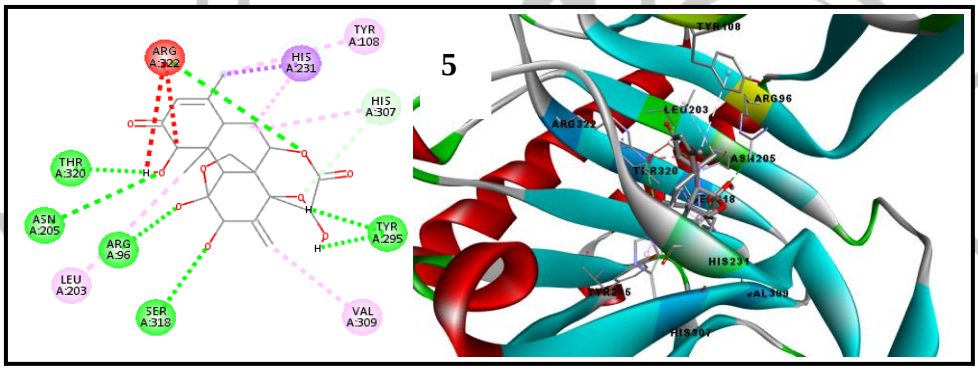
ARG96
LEU109
ARG316
SP233
TYR295
HIS234
HIS307


5
TYR A:108
ARG A:322
HIS A:231
HIS A:307
THR A:320
ASN A:205
ARG A:96
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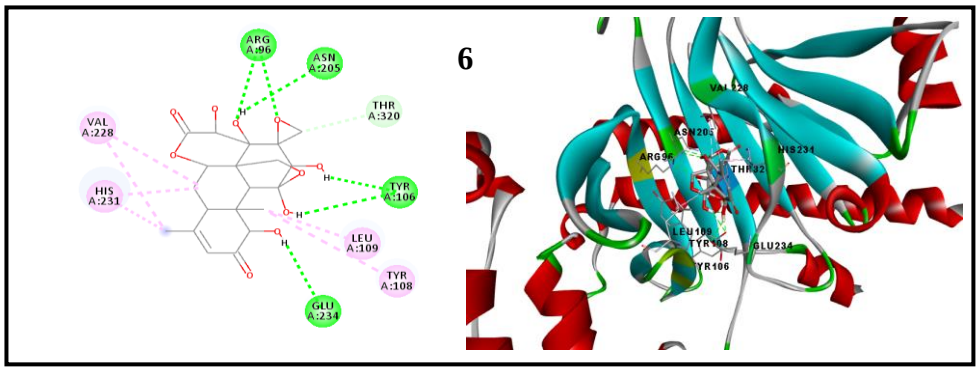
SER A:318
VAL A:309
TYR108
ARG96
LEU203
ARG322
ASN205
TYR320
HIS234


6
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ASN A:205
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HIS A:231
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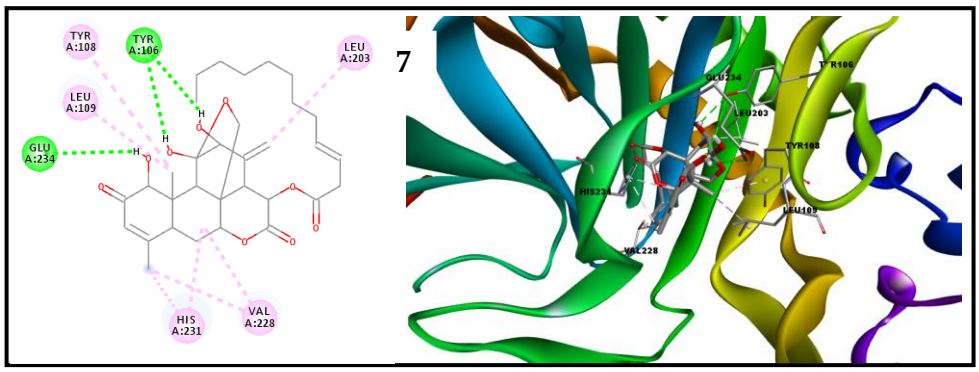

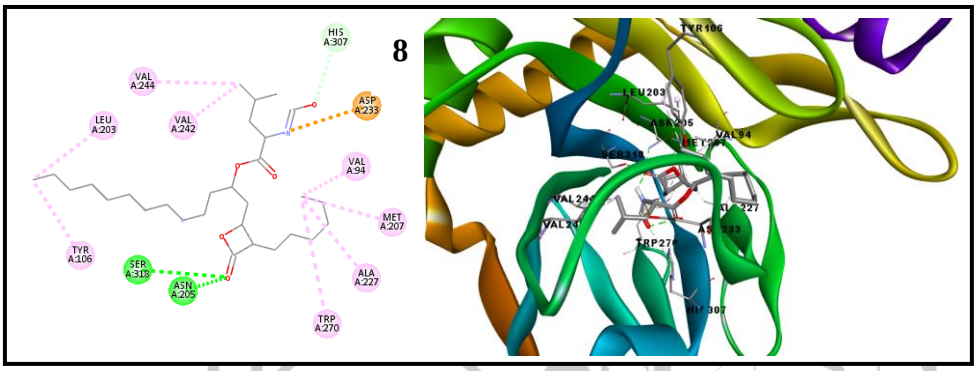

Figure 2: 2D and 3D docking result visualization of test and control ligands with FTO (4IE5) reseptor : (1)eurycomalactone; (2)eurycomanol; (3)laurycolactone; (4)longilactone; (5)pasakbumin A; (6)pasakbumin B; (7)quassinoid, (8)orlistat

Ligands which have potential as anti-obesity were examined by using Lipinski's rule of five. According to the Lipinski's rule, a compound can be used as a drug candidate if it meets the following criteria : its molecular weight is not more than 500 g/mol, the hydrogen acceptor is not more than 10, the hydrogen donor is not more than 5, and the LogP is not more than 5 (Lipinski et al, 2000). Of the three ligands tested, eurycomalactone and laurycolactone compounds met Lipinski requirements and could be used as candidates for anti-obesity drugs. The result can be seen in Table 2.

Table 2: Lipinski's rule of five prediction results

Compounds	Molecular weight	Log P	Hydrogen donor	Hydrogen acceptor
Eurycomalactone	348	2.629	2	6
Eurycomanol	410	3.001	3	9
Laurylactone	304	1.950	1	5
Pasakbumin A	408	2.807	2	9
Quassinoid	572	6.064	2	9

All compounds that meet the Lipinski's rule of five are examined for toxicity and ADME by using the pre-ADMET prediction. The results show that the eurycomalactone compound has a medium permeability to Cac0-2 cell, the

cells responsible for the the absorption process of drugs given orally. The value of %HIA 87.62 shows that this compounds can be well absorbed by the human intestine. The toxicity prediction did not show positive results both mutagen and carsinogen. As for eurycomanol, laurycolactone, and pasakbumin A, the prediction of toxicity shows positive results in causing cancer and mutation. Pre-ADMET prediction results can be seen in Table 3.

Table 3: Pre-ADMET prediction results

Compounds	ADME			Toxicity	
	Caco-2 cell	%HIA	%Plasma protein binding	carsinogenicity	mutagenicity
Eurycomalactone	21.02	87.62	47.21	Negative	Negative
Eurycomanol	19.97	29.25	32.16	Positive	Positive
Laurycolactone	18.66	92.40	52.63	Positive	Positive
Pasakbumin A	20.02	37.40	33.30	Positive	Positive

CONCLUSION

Docking for compound in *M.asiatica* has been successfully carried out against FTO reseptor as antiobesity. Seven compound contained in *M.asiatica* were compared with their interaction with the orlistat patent drug against FTO reseptor. Based on research that has been done, it is known that the compound which has the potential as an antiobesity is eurycomalactone. Ki and ΔG results show better values than orlistat control drugs, fill the Lipinski's rule of five criteria and pre-ADMET prediction show good results without causing the risk of carsinogen and mutagen. It is necessary to modified the structure in order to get a better results.

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