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In Silico Study Of Curcuminoid Compounds In Turmeric (Curcuma Longa) Plants As Halal Anticoagulant Active Ingredients

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In Silico

A b s t r a c t

Background: *Enoxaparin as anticoagulant, which is obtained by depolymerizing the base of heparin benzyl ester which is derived directly from the intestinal mucosa of pigs so that its use triggers a lot of controversy by Muslims. The mechanism of action of enoxaparin is to act as an antithrombin III catalyst which functions to inhibit the formation of blood clots by factor X. The curcumin compound in turmeric is known to have the ability as an anticoagulant drug by inhibiting the formation of factor Xa by factor X.* ***Objective****: This study aimed to predict physicochemical properties, predicted toxicity, and predicted the antiviral activity of eight curcumin-derived compounds in turmeric against antithrombin III receptors (GDP ID: 1R1L) and factor X (GDP ID: 5VOF).* ***Methods****: Prediction of physicochemical properties is carried out using the SwissADME application and referring to Lipinski's five laws. Furthermore, the toxicity class was carried out using the pkCSM Online Tool and Protox Online Tool applications. Prediction of the antiviral activity of compounds was carried out using the Molegro Virtual Docker (MVD) application.* ***Results:*** *The results of the LD50 value and the classification of toxicity classes were classified according to GHS. Eight compounds derived from curcumin belong to toxicity classes 4 and 5. Antithrombin III receptors (GDP ID: 1R1L) and factor X (GDP ID: 5VOF were said to be valid because they had RMSD values below < 2 Å.* ***Conclusion:*** *The results showed that cyclocurcumin compounds were predicted to have good potential anticoagulant activity.*

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INTRODUCTION

Thrombosis is a condition when there is a reduction in the flow of blood fluid in the blood vessels that occurs due to the process of forming blood clots.[1] Complex interactions can arise due to this process and will manifest into several disorders in the blood vessels, one of which is *venous thromboembolism* (VTE). VTE is a condition in which a thrombus forms in a vein. The frequency of *Deep Vein Thrombosis* (DVT) in Indonesia varies from 10% to 26% in patients admitted to the hospital with inpatient therapy and *Pulmonary Embolism* (PE)causes 10% death in the hospital. Meanwhile in Europe, according to data from the *European Society of Cardiology* (ESC) estimated that there were 317,000 deaths (out of a total population of 454.4 million people in six European countries) due to VTE in 2004. Based on the prevalence data, it shows that VTE is still a deadly disease.[2]

At present, several drugs have been found as anticoagulant therapy. One of the most commonly used anticoagulant drugs is Heparin. Heparin has a mechanism of action by becoming an antithrombin III (AT-III) catalyst which will inhibit the formation of protein factor Xa (FXa), then if that happens then thrombin will not form from prothrombin and fibrin will not form from fibrinogen. However, the use of these synthetic drugs is also not free from the side effects that these drugs have. *Heparin Induced Thrombocytopenia* (HIT) is an example of a side effect of using Heparin. HIT is caused by an immunological reaction that makes platelets the target of an immunological response, resulting in decreased platelets and will lead to thrombocytopenia. Heparin has several derivatives that are commonly used in the medical world, such as enoxaparin, dalteparin, nardroparin, bemiparin, and tinzaparinare.[3]

One of the most widely used derivatives of Heparin is Enoxparine. Enoxaparin Sodium (Clexane and Clexane Forte) is obtained by alkaline depolymerization of Heparin benzyl ester which is derived directly from the intestinal mucosa of pigs [4]. Enoxaparine is also known to have side effects, namely the occurrence of thrombocytopenia or low levels of platelets.[5] In other sources it is also stated that the raw material for enoxaparine uses a mixture of n-acetyl from pork intestine.[6] So that this triggers debate among Muslims for its use and it is necessary to conduct research for the development of anticoagulant drugs from halal ingredients.

Turmeric (*Curcuma longa*) is known to have various benefits in its content. Compounds derived from curcumin in the turmeric plant are believed to have medicinal properties. Previous studies have shown that curcumin and its derivative, bisdemethoxycurcumin, have potential as anticoagulants with a *prothrombin time* (PT) value of 35.2 seconds.[7] Previous reports have not conducted research on other curcumin-derived compounds on factor X and antithrombin III proteins as anticoagulant drugs. Therefore, in this research, curcuminoids will be attached to factor X and antithrombin III proteins *in silico* .

METHODS

Materials

The materials used are factor X (PDB ID: 5VOF) and antithrombin III (PDB ID: 1R1L) downloaded from https://www.rcsb.org/ and the curcuminoids in *Curcuma longa* include bisdemethoxycurcumin, cyclocurcumin, curcumin sulfate, didemethylcurcumin, demethoxycurcumin, dihydrocurcumin, monodemethylcurcumin, tetrahydrocurcumin whose molecular structures were drawn using Chem Bio Draw Ultra version 15.

The tools used include hardware in the form of a set of ASUS laptops with specifications for Intel® Core™ i5 Processor and 8GB RAM and Windows 10 Home Single Language operating system software, *Chem Bio Draw Ultra* version 15 (*CambridgeSoft*), *Chem Bio 3D Ultra* version

15 (*CambridgeSoft*), *Molegro Virtual Docker* version 6.0 (*Molegro ApS*), *SwissADME, pkCSM, and Protox Online Tool.*

Compound Preparation

The 2D molecular structures of the 8 curcumin-derived compounds were drawn using the *Chem Draw Ultra V application* 15. Then, the SMILES code was copied and pasted on the *SwissADME website.* After that, it will be known which compounds that pass the preparation have complied with the five Lipinski rules, TPSA, and the amount of torsion.

***In Silico* Sample Preparation**

Compound sample preparation was carried out by creating a 3D structure of the compound with the *Chem Bio Draw Ultra V program.* 15. Energy minimization was carried out by pressing the *MMFF94→ Calculations→Perform→MMFF94→Minim ization option.* The energy minimization process is carried out to determine the most stable conformational form of the compound. Then stored in the form mol2 {SYBYL2(*.mol2)}. Receptor sample preparation by eliminating water molecules and cofactors in the *native ligand* using the *Molegro Virtual Docker* V.6.0 application .

Docking Method Validation

Docking validation was carried out by docking *native ligands* in the receptor cavity using the *Molegro Virtual Docker V.* 6.0 application. Receptor validation results are interpreted with the *Root Mean Square Deviation* (RMSD) value. The receptor can be said to be valid if it meets the RMSD value criteria of 2Å.[8]

Ligand-Protein Docking

Ligand-protein docking is done by detecting the cavity where the drug will bind or interact with the receptor. Place the 3D structure of the compound into the selected cavity. Docking of compounds on receptors is done automatically by *Molegro Virtual Docker* . The parameter measured is the energy value in the form of a rerank score.

Toxicity Prediction

The prediction of the toxicity of the compounds was done by copying the SMILES code on the *Protox online tool website* (http://tox.charite.de/protox_II/) to predict the LD50 value. Then, the prediction of *ames toxicity* and *hepatotoxicity was carried out using the pkCSM* website (http://biosig.unimelb.edu.au/pkcsm/).

RESULTS

Compound Preparation Results

The compounds physicochemical parameters in this study were the Lipinski rule of five, the *Topological Polar Surface Area* (TPSA) value, the amount of torsion, and the determination as a non-substrate Pgp. The results on non-substrate Pgp parameters are shown in Figure 1.

Parameters with Lipinski's five rules and other physicochemical properties are the next prediction stage. The results preparation of compounds with Lipinski's rule of five parameters and other physicochemical properties are shown in Table 1. There were seven compounds that passed the parameters, namely bisdemethoxycurcumin, cyclocurcumin, didemethylcurcumin, dihydrocurcumin, demethoxycurcumin, monodemethylcurcumin,tetrahydrocurcumin .

Figure 2. Shows the compound forms of the seven curcuminoids derivates that complie physicochemical tests with good grades and complied with Lipinski's five rules and that all curcuminoids are Pgp non-substrate marked with a red code on *boilled-egg.*

Receptor Preparation Results

Downloaded proteins are factor X and antithrombin III with protein codes 5VOF (factor X) and 1R1L (antithrombin III). 5VOF contains the *native ligand* rivaroxaban, while 1R1L contains the *native ligand* peptide compound, Receptor preparation was carried out by eliminating water molecules from the *native*

ligand reference using the *Molegro Virtual Docker V* .6.0 application.

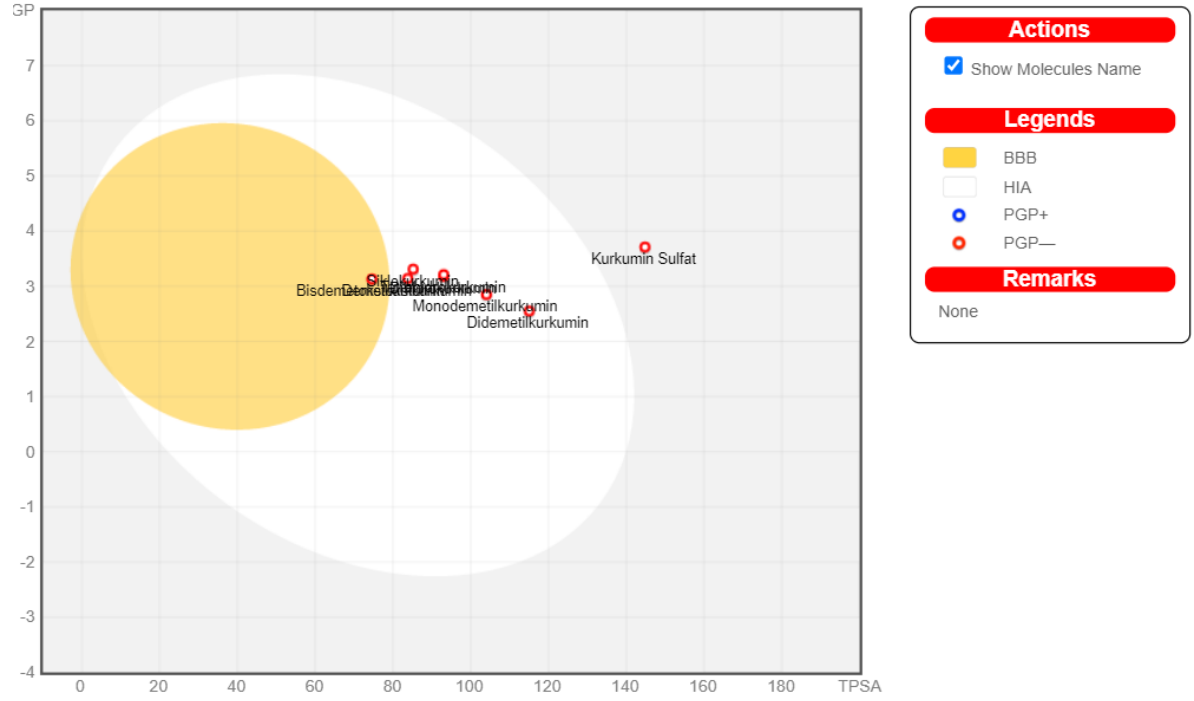
Method Validation

The docking method can be said to be valid if the receptor meets the RMSD value <2Å. [8] Based on the results obtained, cavity 4 on the factor X receptor has the lowest average RMSD value of the other cavities with an average RMSD value of 1.41 Å. Whereas the antithrombin III receptor was selected in cavity 2 which had the lowest average RMSD value with a value of 0.89 Å.

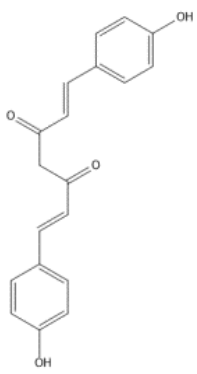
Ligand Bonds to Receptors

The binding of the ligand to the receptor can be seen through the results of the binding energy or *rerank score*.[9] In this study, it was found that the test compounds that received the lowest *rerank score* were cyclocurcumin on factor X and didemethylcurcumin on the antithrombin III receptor. Docking results are shown in Table 2 and Table 3.

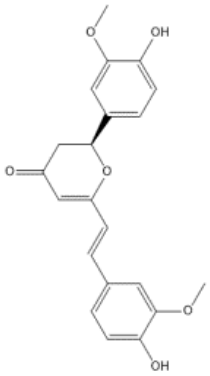
Table 1. Physicochemical prediction results for curcuminoids in turmeric (*Curcuma longa*)



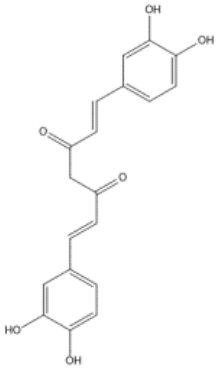
Compound	Lipinski's Rule of Five				TPSA	Torsion	Pgp Substrates
	WM (g/mol)	Log P	HBD	HBA			
Bisdemethoxycurcumin	308,33	2.83	2	4	74.60	6	-
Cyclocurcumin	368.68	2.82	2	6	85.22	5	-
Curcumin Sulfate	448.44	2.42	2	9	144.81	10	-
Didemethylcurcumin	340.33	2.12	4	6	115.06	6	-
Demethoxycurcumin	338.35	3.00	2	5	83.83	7	-
Dihydrocurcumin	370.40	2.97	2	6	93.06	9	-
Monodemethylcurcumin	354.35	2.62	3	6	104.06	7	-
Tetrahydrocurcumin	372.41	3.05	2	6	93.06	10	-



Bisdemethoxycurcumin



Cyclocurcumin



Didemethylcurcumin

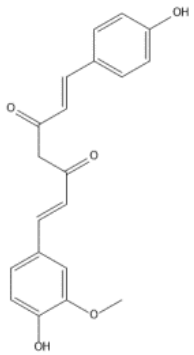
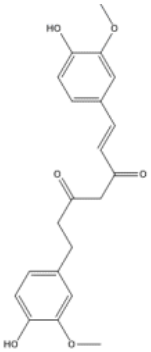
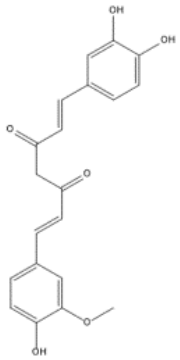
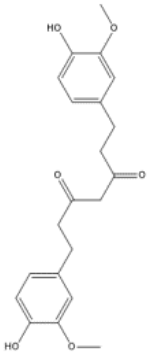
		
Demethoxycurcumin	Dihydrocurcumin	Monodemethylcurcumin
		
	Tetrahydrocurcumin	

Figure 2 Structures of Curcuminoids that Five Lipinski Rule for Physicochemical Predictions

Table 2 Docking Results on Factor X Receptors (PDB ID: 5VOF)

Compound	Mean rerank score
Bisdemethoxycurcumin	-117,138
Cyclocurcumin	-144,783
Didemethylcurcumin	-126,625
Demethoxycurcumin	-120,948
Dihydrocurcumin	-108,939
Monodemethylcurcumin	-124,971
Tetrahydrocurcumin	-131,199
Enoxaparin	-121,203
Rivaroxaban	-135,376

Table 3 Docking results of curcumin-derived compounds and comparator drugs with antithrombin III receptors (PDB ID: 1R1L)

Compound	**Mean rerank score**
Bisdemethoxycurcumin	-134.43
Cyclocurcumin	-121.21
Didemethylcurcumin	-146,557
Demethoxycurcumin	-141.42
Dihydrocurcumin	-145.80
Monodemethylcurcumin	-146,417
Tetrahydrocurcumin	-145,133
Enoxaparin	-73.0333
Native Ligand	-236,583

In this study, there was interaction between the ligand and the active amino acid present in the factor X and antithrombin III receptors. At the factor X receptor, the amino acid is active with 1 hydrogen bond to the native ligand and 2 steric interactions. There are similarities in amino acids in the steric interaction of *native ligands* with amino acids in the curcuminoid compound with the lowest rank score, cyclocurcumin, namely Asp 189, Ile 227, Val 213, Ala 190, and Gln 192. The results of the interaction of amino acid ligands with factor X receptors can be seen in Table 4.

Meanwhile, for the antithrombin III receptor, there is an amino acid similarity between the original ligand and the curcuminoid compound with the lowest *rerank score* , didemethylcurcumin. The amino acids that bind to the same hydrogen bond include Glu 374, Phe 221, and Asn 217. The results of the interaction of the amino acid ligands with the antithrombin III receptor can be seen in Table 5

Compound Toxicity Prediction

The toxicity parameters used were LD50 (*Lethal Dose* 50), *ames toxicity* , and *Hepatotoxicity* . Based on the *Globally Harmonized System* (GHS) the level of toxicity is divided into class I to VI. The toxicity class uses LD50 threshold values of 5, 50, 300, 2000 and 5000 mg/kg body weight.[10] Compounds classified as toxicity class 5 (2000<LD50<5000) are compounds that have low toxicity with the category of possibly being harmful if swallowed, not mutagenic, and not toxic to the liver. Compounds at that level are bisdemethoxycurcumin,didemethyl-curcumin, and tetrahydrocurcumin. While cyclocurcumin, demethoxycurcumin, dihydrocurcumin, and monodemethylcurcumin are in class 4 (300 < LD50 ≤ 2000 mg/kg) with indications of being dangerous if ingested and non-toxic in the *Ames toxicity* and *hepatotoxicity tests*.

Table 4 The Result of The Interaction of The Amino Acid Ligand With The Factor X Receptor (PDB ID: 5VOF)

Compound	Steric Interaction	Hydrogen Bonds
Native ligand (Rivaroxaban)	Glu 97, Lys 96, Phe 174, Thr 98, Trp 215, Tyr 99, Glu 217, Gly 216, Gln 192, Ser 214, Asp 194, Ala 195, Gly 219, Val 213, Cys 191, Ala 190, Ile 227 , Tyr 228, Asp 189, Gly 226.	Gly 216
Enoxaparine	Glu 97, Phe 174, Thr 98, Trp 215, Ala 195, Asp 194, Gly 193, Gln 192, Val 213, Cys 191, Ala 190, Gly 216, Asp 189, Cys 220, Gly 219, Tyr 99	Ala 195, Cys 191, Gly 219, Gln 192, Tyr 99
Bisdemethoxycurcumin	Gly 216 , Gly 219*** , Gln 192*** , Val 213 , Ile 227 , Trp 215	Gly 219** , Gln 192** , Ile 227
Cyclocurcumin	Asp 189 , Ile 227 , Val 213 , Ala 190***, Gln 192*** , Gly 193**	Ala 190, Gly 193
Didemethylcurcumin	Lys 96* , Glu 97*** , Asp 189 , Ala 190*** , Gly 226 , Val 213, Trp 215 , Thr 98	Lys 96, Glu 97, Ala 190, Asp 189
Demethoxycurcumin	Glu 97*** , Tyr 99* , Trp 215 , Thr 98 , Gly 216 , Ala 190*** , Gly 226 , Ser 214 , Asp 189 , Val 213 , Tyr 228 , Ile 227	Ser 214, Asp 189
Dihydrocurcumin	Thr 98 , Phe 174*** , Glu 97*** , Trp 215 , Gly 216 , Asp 189 , Val 213 , Ala 190***	Glu 97, Gly 216* , Asp 189, Ala 190
Monodemethylcurcumin	Glu 146, Gly 193** , Gln 192*** , Asp 189 , Ala 190***, Ile 227	Glu 146, Gly 193, Ala 190
Tetrahydrocurcumin	Thr 98 , Trp 215 , Glu 97*** , Tyr 99* , Ser 214* , Asp 189 , Gly 219***, Ala 190*** , Val 213	Glu 97, Ala 190
Description:	* (same amino acid residue as *native ligand* protein factor Xa), **(Same amino acid residue as enoxaparine/comparison drug), *** (Same amino acid residue as *native ligand* protein factor Xa and enoxaparine/comparison drug).	

DISCUSSION

The aimed of this study was to find candidate curcuminoids in *Curcuma longa* which have potential as halal anticoagulants from nature. Drugs that act as anticoagulants have various mechanisms of action. Enoxaparin works by being a catalyst of the antithrombin III receptor which will inhibit the formation of protein factor Xa (FXa), then if that happens then thrombin will not be formed from prothrombin and fibrin will not be formed from fibrinogen.[3]

Curcumin has shown good results in inhibiting the formation of thrombin in the blood. Compounds derived from curcumin are able to extend blood clotting time in the PT test.[7] The parameters used in this study were to predict physicochemical properties and affinity for factor X and antithrombin III. In addition, toxicity prediction was carried out to determine the safety of curcuminoids.

In the prediction of physicochemical properties there are parameters that follow Lipinski's five rules, where these rules can predict the biological activity of a compound designed for oral administration. According to the Lipinski rules, drugs intended for oral use may not violate more than one of the criteria contained in the Lipinski rules.[11] Compounds that comply with these rules will be predicted to have good permeability in the gastrointestinal tract so that are easily absorbed.[12] Based on these regulations, drug compounds are required to have a molecular weight <500 dalton, log P value <5, number of *hydrogen bond donors* (HBD) <5, and number of *hydrogen bond acceptors* (HBA) <10. In subsequent studies, two additional rules were discovered, aimed at increasing the bioavailability of drugs intended for oral use. These parameters are *Topological Polar Surface Area* (TPSA) <140 Å and total Torque <10.[13] *Polar Surface Area* (TPSA) <140 Å and total Torque <10.[13]

Another physicochemical parameter that is the focus of this research is *P-glycoprotein non-substrate* . *P-glycoprotein* (Pgp) is a transporter protein that plays a role in transporting xenobotics including drug fractions out of the cell against the concentration gradient of the ATP hydrolysis process.[14] P-gp is a member of the ATP binding cassette (ABC) transporter superfamily, which is a determinant of various processes of penetration and absorption of drug compounds. P-gp activity is highly dependent on ATP by forming the P-gp-ATP complex. The function of P-gp is as an efflux transporter that can move structurally unrelated compounds across cellular membranes.[15] A positive result as a Pgp substrate/ inhibitor will be marked with a + symbol in the table, and a result - indicates Pgp is not a substrate.

It was known that all compounds are Pgp non-substrates marked with a red round code on *boilled-egg* . Then it was also known that of the 8 curcuminoid compounds in *Curcuma longa* , only 7 compounds had good results for physicochemical predictions. Curcumin sulfate is known to have a TPSA value of 144.81 Å and has a poor absorption GI level. TPSA values that exceed 144 Å are known to be difficult to penetrate cell membranes because the compound has a surface shape that is too broad and a poor GI absorption level will also be difficult to be absorbed by the blood-brain barrier or by the intestine.[16]

Prior to the ligand docking process, cavities are first determined to detect where the ligand interacts with the receptor. Furthermore, method validation was carried out by docking the *native ligand* in the receptor cavity. The method can be said to be valid if it meets the RMSD value criteria <2Å (Jain and Nicholls, 2008). Based on the results obtained, cavity 4 on the factor X receptor has the lowest average RMSD value of the other cavities with an average RMSD value of 1.41 Å. Whereas the antithrombin III receptor was selected in cavity 2 which had the lowest average RMSD value with a value of 0.89 Å. The results of the method validation can be seen in Table 6. binding energy of a compound with a receptor can be determined through *a rerank score.* [9] The Rerank Score

Table 5 The Result of The Interaction of The Amino Acid Ligand With The Antithrombin III Receptor (PDB ID: 1R1L)

Compound	Steric Interaction	Hydrogen Bonds
Native ligand Antithrombin III	Arg 197, Tyr 220, Lys 222, Phe 221, Phe 372, Ala 371, Ile 219, Asn 376, Lys 370, Asn 217, His 369, Gly 223, Glu 374	Lys 222, Arg 197, Gly 223, Glu 374, Lys 370, Asn 217, Asn 376, Ile 219, Phe 372, Phe 221
Enoxaparine	Lys 139, Asn 135, Ser 137, Lys 275, Lys 133, Ala 134, Lys 136, Ser 138, Arg 132, Val 141, Leu 140	Leu 140, Lys 136, Ser 137, Ala 134, Ser 138
Bisdemethoxycurcumin	Phe 221*, Phe 372*, Arg 197*, Ile 219*, Ser 82, Asn 217*, Lys 222* , Gly 379, Glu 374*	Phe 221* , Ser 82, Gly 379
Cyclocurcumin	Ile 219* , Phe 422, Phe 372*, Glu 374*, Arg 197*, Lys 222*	Ile 219*, Lys 222*
Didemethyl Curcumin	Gly 379, Arg 197*, Glu 374*, Phe 372*, Phe 221*, Ile 219*, Asn 217* , Ser 82	Gly 379, Glu 374*, Phe 221* , Ser 82, Asn 217*
Demethoxycurcumin	Ser 82, Asn 217*, Phe 372*, Tyr 220*, Phe 221*, Glu 374 *, Gly 379	Asn 217*, Glu 374*, Phe 221*
Dihydrocurcumin	Phe 422, Ser 82, His 369*, Ile 219*, Phe 221*, Gly 223*	Ser 82, His 369 , Ile 219*, Gly 223*
Monodemethylcurcumin	Phe 368, Val 201, Lys 370*, Ile 219* , Ser 82, Phe 372*, Phe 221*	Phe 368, Ile 219* , Ser 82, Phe 221*
Tetrahydrocurcumin	Glu 374*, Lys 222*, Phe 372* , Phe 422, Thr 218, Asn 217*, Lys 370*, His 369*	Glu 374*, Lys 222*, Asn 217*

Remarks : *(Same amino acid residue as *native ligand* antithrombin III protein).

Table 6 Results of docking validation of factor X receptors (PDB ID: 5VOF) and antithrombin III (PDB ID: 1R1L)

Receptors	Compound	RMSD R1	RMSD R2	RMSD R3	Average
5VOF (H)	Native Ligand	1.33	1.45	1.46	1.41
1R1L(I)	Native Ligand	0.89	0.96	0.84	0.89

value in the MVD application is a calculated value which is a combination of the Moldock value with the addition of various conditions including the steric term which areLennard Jones approximations to the steric energy.[17] *Rerank score* is obtained from calculating the total energy of all bonds. Based on Table 2, it shows that the cyclocurcumin compound has the lowest *rerank score value* compared to the comparator drug compound and *native ligand* on factor X receptors. Meanwhile in Table 3, it shows that the *rerank score value* of *native ligand* has the lowest value, followed by didemethylcurcumin and enoxaparin compounds on antithrombin III. antithrombin receptor. Some compounds that show lower rerank scores than enoxaparin that indicate good result.[18]

In the factor X receptor, it was known in previous studies that the rivaroxaban structure of the S1 pocket, Cys191 disulfide bonds hold loops 189–195 and loops 214–220 to form a dense S1 pocket with backbone residues Ala190, Gln192, Val213, and Ile227 which contribute the most major on rivaroxaban binding.[19] Cyclocurcumin as a curcuminoid compound with the lowest *rerank score* has the same amino acids as the *native ligand* , namely, Asp 189 which is in the hydroxyl group, Val 213, Ala 190, and Gln 192 which are in the methyl group, and Ile 227 which is in the ketone group. Then on the antithrombin III receptor it has been known in previous studies that there are 3 amino acids from heparin that are able to bind properly to antithrombin III namely, Lys 125, Lys 114, and Asn 135.[20] It was found that, didemethylcurcumin as a curcumin derivative compound with the lowest value has the same amino acid on Asn 135.[20] According to Puspaningtyas (2013) the more amino acids that are bound, especially in hydrogen bonds, the stronger the bond and the lower/stable the *energy score.*[21]

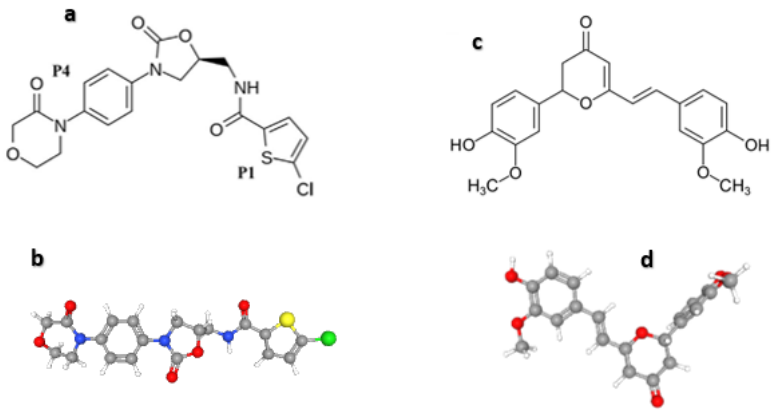


Figure 3 (a) 2D Structure of Rivaroxaban; (b) 3D Structure of Rivaroxaban; (c) 2D Structure of Cyclocurcumin (d) 3D Structure of Cyclocurcumin

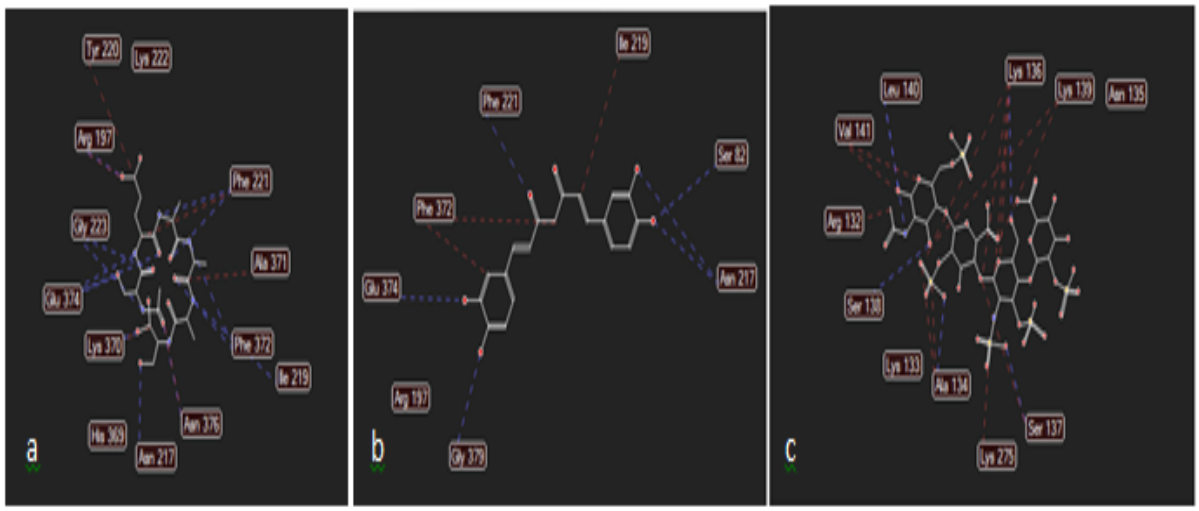


Figure 4 The Results Of The Amino Acid Interaction Between The Antithrombin III Receptor (PDB ID: 1R1L) And The Test Compound (a) Native Ligand; (b) Didemethylcurcumin; (c) Enoxaparin

Toxicity is a condition indicating the presence of poison or toxic effects on the ingredients contained in a drug preparation. LD50 is the concentration of a compound that can cause 50% death in experimental animals. *Ames toxicity* test is a test used to determine the presence of mutagenic potential in a compound. If a positive test result is obtained, it indicates that the compound is mutagenic and can act as a carcinogen. The *hepatotoxicity test* aims to determine the ability of a compound to damage the liver.[22] Based on the results of Table 7, it shows that cyclocurcumin, demethoxycurcumin, dihydrocurcumin, and monodemethylcurcumin are in class 4 (300 < LD50 ≤ 2000 mg/kg) which have dangerous information if ingested, while bisdemethoxycurcumin, didemethyl curcumin, and tetrahydrocurcumin compounds show class 5 (2000). < LD50 ≤ 5000 mg/kg) has the information that it can be harmful if swallowed. Then in the *ames toxicity* and *hepatotoxicity table* it is known that all curcumin-derived compounds showed negative results so that it can be ensured that all curcumin-derived compounds do not have mutagenic potential and damage the liver.

CONCLUSION

The compounds bisdemethoxycurcumin, cyclocurcumin, didemethylcurcumin, dihydrocurcumin, demethoxycurcumin, monodimethylcurcumin, and tetrahydrocurcumin have fulfilled all physicochemical parameters and belong to the toxicity class 4 and 5, which is still quite safe as a drug candidate. Another toxicity prediction shown that all compound do not cause mutagenic potential and damage the liver. These compounds have a fairly good *rerank score* , among the best are cyclocurcumin on factor X and didemethylcurcumin on antithrombin III. Therefore, these compounds can be used as alternative candidates for halal anticoagulant drugs derived from natural ingredients.

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