MOLECULAR DOCKING ANALYSIS OF SELECTED *Curcuma xanthorrhiza* CONSTITUENTS AS POTENTIAL ANTICANCER DRUG

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ABSTRACT

Stress conditions will trigger the histone hyperacetylation process due to p300/CBP histone acetyltransferase (PCAF HAT) constantly transferring acetyl groups from acetyl-CoA to conserved lysine residues on histone proteins to form ε-N-acetyllysine. This can be a cause of cancer. The purpose of this study was to investigate the potential mechanisms and inhibition of PCAF HAT by chemical components of *C. xanthorrhiza* namely, curcumin, demethoxycurcumin, bisdemethoxycurcumin, and xanthorrizhol using *in silico*, the molecular docking method. Results showed that the components of *C. xanthorrhiza* as ligands have the capability to inhibit the binding of acetyl-CoA to histone. These results can be used to predict the inhibitory mechanisms exhibited by *C. xanthorrhiza* components, as competitive and noncompetitive substances. Our hypothesis was that *C. xanthorrhiza* components resemble a substrate, leading to prevention of the natural substrate (histone) to bind to the enzyme, and hence block the product formation. The smallest free Gibs energy was exhibited by curcumin on chain B and by bismethoxycurcumin on chain A, with values of -8.8 and -8.4 kcal/mol, respectively.

Keywords: *C. xanthorrhiza*, curcumin, PCAF HAT, xanthorrhizol

INTRODUCTION

Curcuma xanthorrhiza, in Indonesia known as *temulawak*, also called Javanese turmeric or Java ginger, is a medicinal plant belonging to the ginger family (Zingiberaceae). The plant is originated in Indonesia, on Java Island, then spread to several places such as Thailand, the Philippines, Sri Lanka and Malaysia. *C. xanthorrhiza* is a low-growing plant with rhizome which is similar to ginger (Salleh *et al.* 2016).

In Indonesia, rhizome is the only part of the plant generally utilized to make a herbal brew called jamu godog. The *C. xanthorrhiza* rhizome contains 1.6 - 2.2% curcumin, 48 - 59.64% starch, and 1.48 - 1.63% essential oils and is believed to have the ability to improve kidneys function kidney and has anti-inflammatory properties. A commercial grade of *C. xanthorrhiza* contains 77% curcumin, 17% demethoxycurcumin and 3% bisdemethoxycurcumin (Huang *et al.* 1995). The rhizome of *temulawak* can also be used as acne remedy, appetite stimulant, anti-cholestrerol, anti-inflammatory, anemia remedy, anti-oxidant for cancer prevention, and anti-microbial agent.

C. xanthorrhiza has great potential in pharmacological activities, namely anti-inflammatory, anti-immunodeficiency, anti-bacterial, anti-fungal, anti-oxidant, anti-infective and anti-cancer (Chattopadhyay *et al.* 2004; Joe *et al.* 2004). The fresh rhizome of *C. xanthorrhiza* was reported to contain large amounts of sesquiterpenoids followed by curcuminoids and monoterpenoids. Xanthorrhizol as the major natural sesquiterpenoid in *C. xanthorrhiza* rhizome has been indicated as having the ability to inhibit the proliferation of the human breast cancer cell line, MCF-7, with an EC50 value of 1.71 μg/mL. Furthermore, it was suggested that the anti-proliferative effects of xanthorrhizol on MCF-7 cells involves apoptosis induction through modulation of bcl-2, p53 and PARP-1

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protein levels (Cheah *et al.* 2006). In addition, curcumin, demethoxycurcumin and bisdemethoxycurcumin isolated from the methanol extracts of *C. xanthorrhiza*, exhibited strong antioxidant activity indicated by their ability to inhibit copper-mediated oxidation of low-density lipoprotein (LDL) and may potentially be used as a natural sources of cardiovascular protective agents (Jantan *et al.* 2012). In the present study, the effect of curcumin, bismetoxycurcumin, bisdemethoxy-curcumin and xanthorizol on histone acetyltransferase is investigated by using molecular docking method in a search for potential anti-cancer candidates.

Molecular docking is a computational modeling of the structure of complexes formed by two or more interacting molecules which can be used to predict the binding orientation of drug candidates to their protein targets. The information on preferred orientation can be used to predict the strength of binding or affinity between two molecules using scoring functions (Monika *et al.* 2010).

Knowledge of affinity of these selected *C. xanthorrhiza* components to histone acetyltransferase may be useful for predicting their inhibitory activity on the enzyme. The use of the molecular docking method provides the benefit of narrowing the focus of research, saving on research costs, and streamlining research time and cost (Sharma *et al.* 2010). It should be noted, however, that molecular docking is not as accurate as an experimentally determined structural orientation, and therefore, interaction details of the detailed *C. xanthorrhiza* components to histone acetyltransferase need to be characterized through X-ray crystallography or nuclear magnetic resonance (NMR) spectroscopy study (Gupta *et al.* 2011).

In addition, most of the docking approaches are based on the rigid receptor hypothesis in which the receptor is held rigid preventing considerable effects of induced-fit within the binding site (Pérez & Tvaroška 2014). This may cause incorrect ligand binding modes which can be overlooking the drug lead potential (Monika *et al.* 2010).

Histone acetyltransferases (HATs) are group of enzymes responsible for histone and non-histone protein acetylation. HATs include p300/CREB-binding protein (CBP), MYST, and GNAT family members. The GNAT family members include the p300/CBP-associated factor (PCAF). HATs are critical regulators of carcinogenesis. Cancer genome studies have identified HATs as common targets for mutations in cancer diseases (Sun *et al.* 2015). Acetylation of histones has been shown to play an essential role in the epigenetic regulation of gene expression (Gupta *et al.* 2011).

Furthermore, the balance of histone acetylation and deacetylation is critical in the regulation of gene expression. Histone acetylation induced by HATs is associated with gene transcription, while histone hypo-acetylation induced by histone deacetylase (HDAC) activity is associated with gene silencing. Altered expression and mutations of genes that encode HDACs have been linked to tumor development (Ropero & Esteller 2007).

Additionally, several HATs, including p300, CBP, and PCAF are indicated to directly regulate the activity of tumor suppressor protein, p53 through acetylation. The PCAF complex is known to acetylate histones and transcriptional regulators and modulate activities of several tumor suppressors and oncogenes (Love *et al.* 2012).

In developing molecules for HAT inhibitor, it is important to consider that HATs are bi-substrate enzymes, in that, they catalyze reactions between two substrates, the cofactor acetyl-CoA and a lysine-harboring substrate (Wapenaar & Dekker 2016).

MATERIALS AND METHODS

Preparation of Ligand

The test ligands used were curcumin, demetokxycurcumin, bismetoxycurcumin and xanthorizol in *C. xanthorrhiza* which had the ability to inhibit PCAF HAT. Ligands were downloaded through the PubChem Compound website. The structure of the downloaded ligand analyzed the ligand liabilities properties by using Lipinski rule parameters (Lipinski *et al.* 2001).

Preparation of Molecular Receptors

The receptor used was the one for PCAF HAT. This receptor was downloaded from the Protein Database Bank (PDB) website with

1CM0 code. The downloaded receptor had two chains (A and B).

Molecular Docking

The downloaded molecular docking process was implemented by using software AutoDock Vina 1.5.6. The receptor protein and ligands used were first modified from .pdb to .pdbqt. Molecular docking was accomplished by docking the ligand to the PCAF HAT receptor by filling in the appropriate docking coordinates. The molecular docking process was carried out 20 times to get the best Gibbs free energy.

Analysis on Docking Results

The latch holding area of the receptor was changed from the format .pdbqt to .pdb using the Discovery Studio 3.5 Client software. The file was then analyzed using Ligplot + 1.4.5 software. Analysis results showed the interaction between ligand and protein. Such interactions include hydrogen bonding, hydrophobic interaction and bond distance. Interaction results were visualized using Ligplot + 1.4.5 software.

RESULTS AND DISCUSSION

Ligands Characteristics Based on Lipinski Rule

The compounds structure in *C. xanthorrhiza*, which was used as ligands, was analyzed using the Lipinski rule (Table 1). This rule estimates the permeability of the ligand to the membrane and the ease of the ligands to be absorbed in the body. Criteria (1) molecular weight less than 500 g/mol, (2) lipophilicity of the compound, logarithmic partition coefficient, less than 5.0, (3) the number of donor hydrogen atoms in the hydrogen bonds of less than 5.0, and (4) the number of hydrogen atom acceptors for forming a hydrogen bond of less than 10. These four parameters were obtained from the PubChem database (http://pubchem.ncbi.nlm.nih.gov).

Lipophilicity is one of the important physicochemical factors in pharmaceutical drug absorption (Edwards & Price 2010). It is associated with gastrointestinal epithelial cell membrane (Alavijeh *et al.* 2005), which affects the rate of absorption of chemical substances in the gut through active diffusion (Mannhold *et al.* 2007). Table 1 shows that the *C. xanthorrhiza* component acting as a ligand has a partition coefficient in the optimum range. The results indicated that the ligands were easily absorbed by the body, because it had a value less than 5, while the number of acceptors of strong hydrogen bond was less than 10. The experimental results showed that all tested ligands had acceptor and donor hydrogen bonds in the optimum range, so that the ligands had a good absorption rate.

Gibbs Free Energy Ligand with PCAF HAT

Different Gibbs free binding modes were the result of ligand molecules with PCAF HAT using Vina Autodock software. The most negative values indicate a bond between strong and stable receptor ligands. The test results showed that the most negative results in the curcumin ligand (demethoxycurcumin) were bound to PCAF HAT B chains with Gibbs -8.8 free energy values. Gibbs values are presented in Figure 1 and Table 2.

Table 1 Ligands characteristics based on Lipinski Rule

Structure name	Structure formula	Molecular weight (g/mol)	Log P	Σ Donor hydrogen bond	Σ Acceptors hydrogen bond
Curcumin	$C_{21}H_{20}O_6$	368.38	3.2	2	6
Demetoxycurcumin	$C_{20}H_{18}O_5$	338.35	3.3	2	5
Bisdemetoxycurcumin	$C_{19}H_{16}O_4$	308.33	3.3	2	4
Xanthorrhizol	$C_{15}H_{22}O$	218.33	5.1	1	1

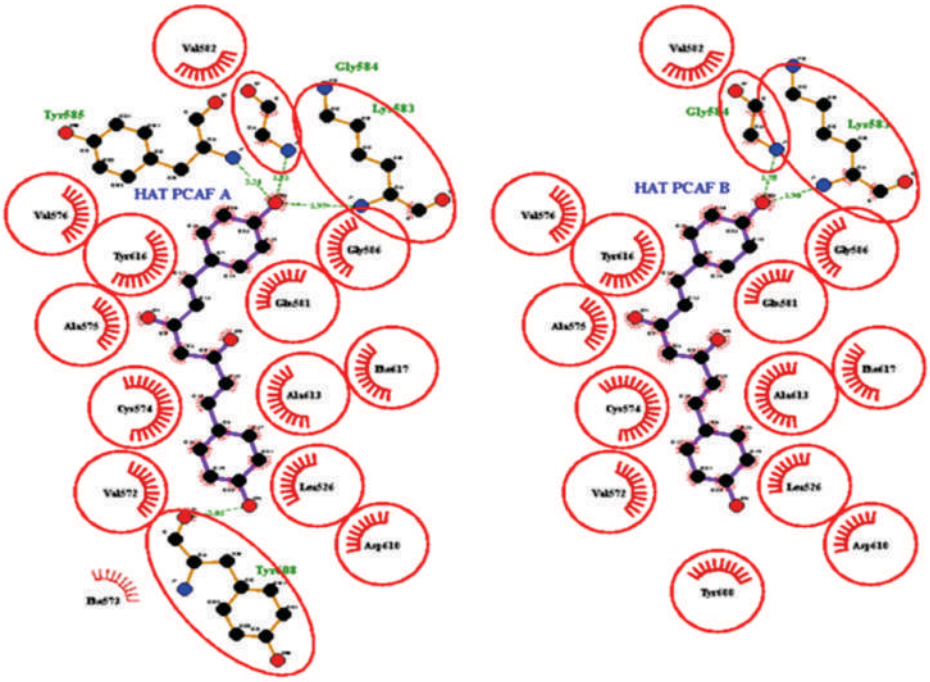

Figure 1 Result of demethoxycurcumin docking with PCAF HAT

Table 2 Gibbs free energy ligand *C. xanthorrhiza* components

Structure name	Structure formula	A	B
Curcumin	$C_{21}H_{20}O_6$	-8	-8.8
Demetoxycurcumin	$C_{20}H_{18}O_5$	-7.3	-8.5
Bisdemetoxycurcumin	$C_{19}H_{16}O_4$	-8.4	-8.6
Xanthorrhizol	$C_{15}H_{22}O$	-8.1	-8.1

Notes: Letter A denotes the PCAF HAT A; letter B denotes the PCAF HAT B

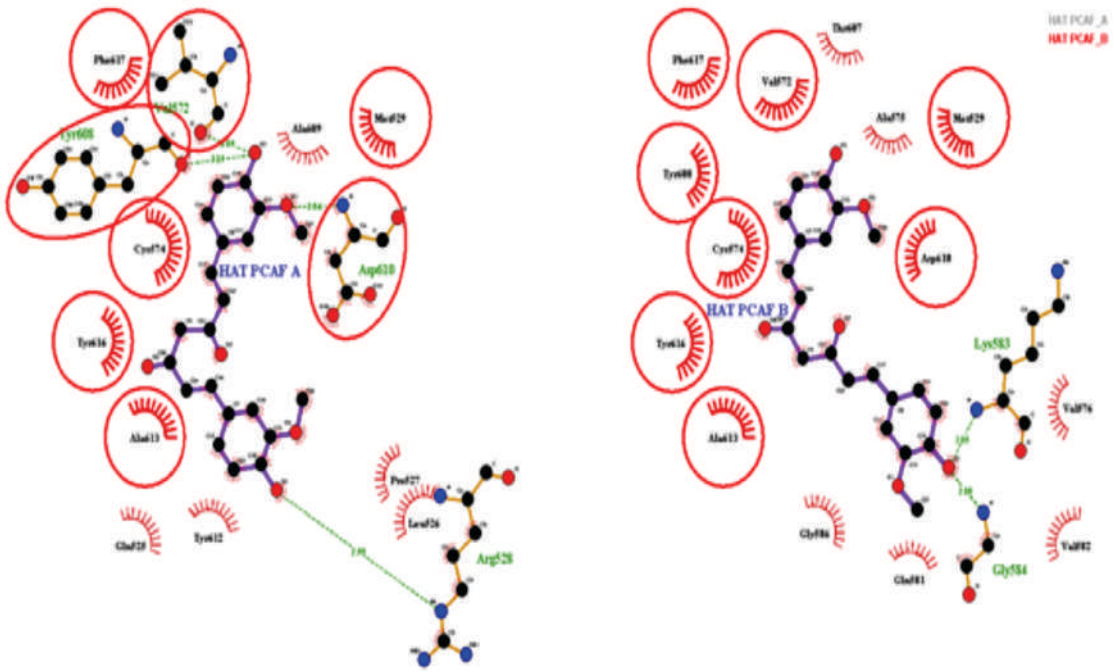

Figure 2 Result of bisdemethoxycurcumin docking with PCAF HAT

The docking result between molecular components of ginger (bisdemethoxycurcumin) with PCAF HAT enzyme showed negative Gibbs free energy (Fig. 2). This indicated that every component of ginger was able to bind PCAF HAT spontaneously and strongly. The highest value of Gibbs free energy in this study was curcumin attached to PCAF HAT on ring B with ΔG -8.8 kcal/mol, while the lowest Gibbs energy value was demethoxycurcumin bound to calculate PCAF HAT ΔG -7.3 kcal/mol. This suggested that curcumin interactions were more spontaneous and stronger than other ligands and demethoxycurcumin.

The results also showed that the *C. xanthorrhiza* component with the PCAF HAT A chain tended to be lower than the bond with PCAF HAT B chain. These results are similar to those done *in silico* by Vinsentricia (2015). These results suggested that the PCAF HAT B chain has a better stability than PCAF HAT A chain that interacts with ligands and proteins, which is similar to research results of Ghizzoni *et al.* (2010) and Dekker *et al.* (2009). Studies conducted by Clements *et al.* (1999) produced two chains with different crystal lattice contacts. According to Martz (2003), the difference in crystal lattice contact allows differences in protein conformation. The protein conformation affects the specificity and affinity of binding, which makes a difference in conformation, Gibbs free energy and the bonds between chains A and B.

Interaction of Ligands of Active Compounds of *C. xanthorrhiza* with PCAF HAT

A visualized binding mode was obtained by using Ligplot + software from a ligand molecule with PCAF HAT, indicating that the hydrogen bond (along with the bonding distance) and the hydrophobic bond were located at less than 5 Å. The binding of demethoxycurcumin with the PCAF HAT B chain had more than 5 bonds, whereas the lowest hydrogen bond count was the bond between xanthorrhizol with the PCAF HAT A and PCAF HAT B chains of 0 bonds. The bonding interaction between *C. xanthorrhiza* component and the PCAF HAT can be seen in Table 3.

Table 3 Ligands interaction with PCAF HAT at radius less than 5 Å

Ligands	HAT PCAF Chain	Σ Hydrogen Bond	G (Cal/mol)	Distance Hydrogen Bond (Å)	Residue	Ligands Functional Groups	Residue involved in <5 Å
Curcumin	A	4	-8	3.09	Val572	OH3	Phe617, Cys574 Tyr616, Ala613, Gln525, Tyr612, Leu526, Pro527, Met529, Al609
				3.19	Tyr608	OH3	
				3.04	Asp610	OH1	
				2.99	Arg528	OH4	
	B	2	-8.8	2.85	Lys583	OH3	Val576, Val582, Gln581, Gly586, Ala613, Tyr616, Cys574, Val572, Tht607, Ala575, Met529, Asp610
				2.8	Gly584	OH3	
Demetoxycurcumin	A	1	-7.3	2.9	Tyr608	OH5	Phe617, Val572, Cys574, Phe573, Leu526, Asp610, Arg528, Pro527, Gln525, Tyr616, Ala613
	B	5	-8.5	3.01	Lys583	OH1	Tyr585, Val576, Gln581, Phe617, Glu580, Gly586, Cys574, Leu526, Asp610, Tyr616, Ala613
				3.1	Val582	OH1	
				2.99	Gly584	OH1	
				3.2	Gly584	OH1	
				2.95	Val572	OH5	

Table 3 (Continued)

Bisdemetoxycurcumin	A	4	-8.4	2.97	Lys583	OH3	Aps610, Leu526, Ala13, Phe617, Gln581, Gly586, Val582, Val576, Tyr616, Ala575, Cys574, Val572, Phe573
				2.82	Gly584	OH3	
				3.31	Tyr585	OH3	
				3.02	Tyr608	OH3	
	B	2	-8.6	2.9	Lys583	OH3	Asp610, Leu526, Ala613, Phe617, Gln581, Gly586, Val582, Val576, Tyr616, Ala575, Cys574, Val572
				2.78	Gly584	OH3	
Xanthorrhizol	A	0	-8.1				Gly586, Tyr616, Cys574, Phe617, Val572, Asp610, Ala613
	B	0	-8.1				Gly586, Tyr616, Cys574, Phe617, Val572, Asp610, Ala613, Phe573

In two-dimensional visualization, the dotted green line showed the hydrogen bond between the ligand and the receptor protein, whereas the arc with red dashed lines indicated hydrophobic bonds formed at a distance less than 5 Å. Visualization was performed on the components of *C. xanthorrhiza* presented on Figure 1 (demethoxycurcumin), Figure 2 (bisdemethoxy-curcumin), Figure 3 (curcumin) and Figure 4 (xanthorrhizol).

The docking method performed on curcumin with the PCAF HAT A chain produced hydrogen bonds on residues Val572, Tyr608, Asp610, and Arg528 involved in the binding of acetyl-CoA by PCAF histone acetyltransferase. Residues involved in hydrophobic bonds were residues having acetyl-CoA bonding functions, including Phe617, Cys574, Tyr616, Ala613, Gln525, Tyr612, Leu526, Pro527, Met529 and Ala 609. The docking method on curcumin with the PCAF HAT chain showed the hydrogen bond on residues Lys583, Gly584 and Val762 was involved in binding of histone by PCAF HAT.

Other residues involved, namely Val576, Val582, Gln581, Gly586, Ala613, Tyr616, Cys574, Val572, Tht 607, Ala575, Met 529 and Asp610 were residues involved in acetyl-CoA binding by PCAF HAT (Clements *et al.* 1999). These results suggested that curcumin has the ability to inhibit PCAF HAT in binding with acetyl-CoA both the A and B chains. However, bonding to the B chain was much stronger than bonding to the A chain, which was proven by a very short bonding distance of the B chain compared to that of the A chain.

The hydrogen bonds occurring in the bonding to the B chain had a tendency to bind stronger histones. This was characterized by hydrogen bonds that were close to Lys583 (2.85 Å) and Gly584 (2.8 Å) residues which indicated stronger bonds. The binding was stronger than the binding of acetyl-CoA with curcumin to the PCAF HAT A chain. The large number of amino acid residues resulting in inhibition against the PCAF HAT A chain made it quite stable.

The docking method performed on demetoxycurcumin with the PCAF HAT A chain produced hydrogen bonds on the Tyr 608 residue involved in the binding of acetyl-CoA by PCAF histone acetyltransferase. Residues involved in hydrophobic bonds were residues that have acetyl-CoA binding functions, including Phe617, Val572, Cys574, Phe573, Leu526, Asp610, Arg528, Pro527, Gln525, Tyr616 and Ala613. The docking method on demethoxycurcumin with the PCAF HAT B chain showed the hydrogen bonds on residues Lys583, Val582, Gly584 and Val572 involved in binding of histone by PCAF HAT.

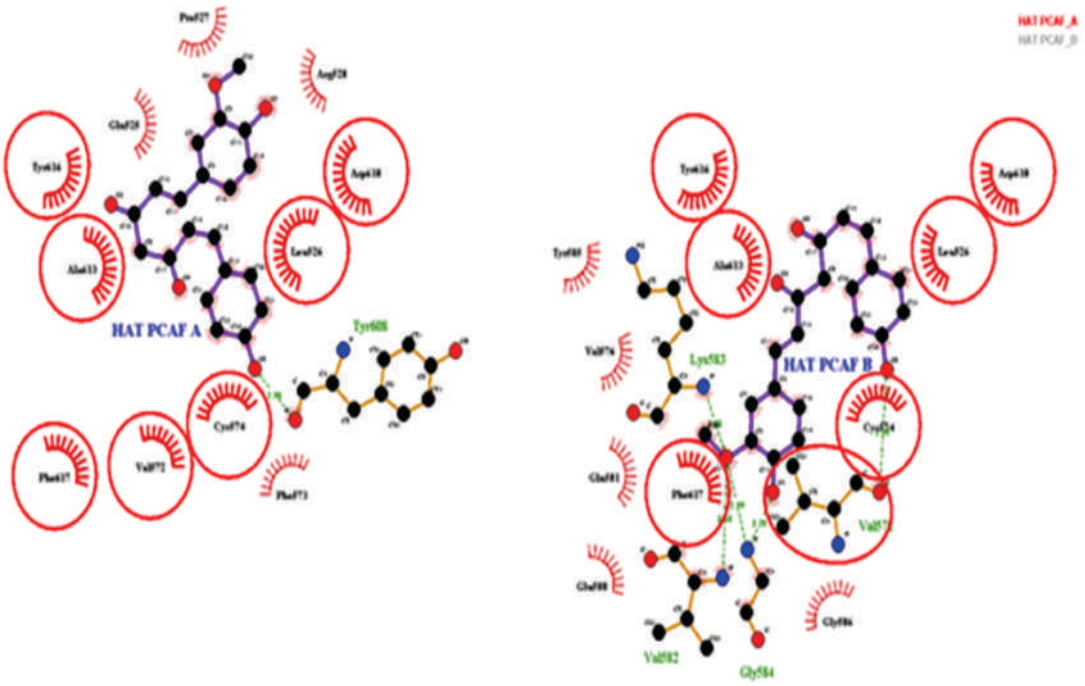

Figure 3 Result of curcumin docking with PCAF HAT

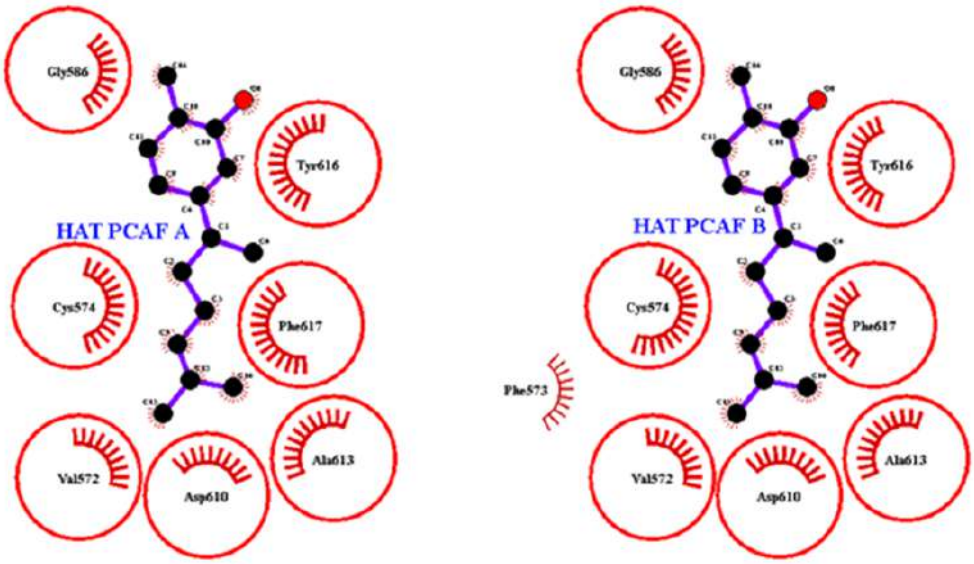

Figure 4 Result of xanthorrhizol with PCAF HAT

Other residues involved were Tyr585, Val576, Gln581, Phe617, Glu580, Gly586, Cys574, Leu526, Asp610 and Ala613, which were residues involved in acetyl-CoA bonding by PCAF HAT (Clements *et al.* 1999). These results suggested that demetoxycurcumin has the ability to inhibit PCAF HAT binding with acetyl-CoA in both A and B chains. However, the bond to A chain was much stronger than that to B chain. This was evident from a very short bonding distance of the A chain compared to the B chain.

The hydrogen bonds that occurred in the bonding to the A chain had a tendency to bind stronger histones. This was characterized by a hydrogen bond that was closer to the Tyr 608 residue (2.9 Å), thus, indicating a stronger bond. The binding was stronger than the binding of

acetyl-CoA with demetoxicurcumin in the PCAT HAT A chain. However, the large amount of amino acid residues resulting in inhibition against the PCAF HAT B chain was quite stable and resulted in strong bonds occurring in the PCAF HAT B chain.

The docking method performed on bisdemethoxycurcumin with the PCAF HAT A chain produced hydrogen bonds on residues Lys583, Gly584, Tyr585 and Tyr608 which were involved in the binding of acetyl-CoA by PCAF histone acetyltransferase. Residues involved in hydrophobic bonds were residues having acetyl-CoA binding functions, including Asp610, Leu526, Ala613, Phe617, Gln581, Gly586, Val582, Val576, Tyr616, Ala575, Cys574, Val572 and Phe573. Docking method on bisdemethoxycurcumin with the PCAF HAT B chain showed hydrogen bonds on Lys583 and Gly584 residues which were involved in the histone binding by the PCAF HAT.

Other residues were also involved, namely Asp610, Leu526, Ala613, Phe617, Gln581, Gly586, Val582, Val576, Tyr616, Ala575, Cys574 and Val572A, which were residues involved in acetyl-CoA bonding by PCAF HAT (Clements *et al.* 1999). These results suggested that bisdemethoxycurcumin has the ability to inhibit PCAF HAT binding with acetyl-CoA in both A and B chains, but the bonding to B chain was much stronger than that to A chain. This was evident from the very short bonding distance of B chain compared to A chain.

The hydrogen bonds that occurred in the bonding to B chain had a tendency to bind stronger histones. It was characterized by a hydrogen bond which was close to the length of Gly584 (2.78 Å) and Lys583 residues (2.9 Å), which indicated a strong bond. The binding was stronger than the binding of acetyl-CoA with bisdemethoxicurcumin in the PCAF HAT B chain. However, the large number of amino acid residues resulting in inhibition against the PCAF HAT A chain was quite stable and this resulted in strong bonding occurring in the PCAF HAT A chain.

The docking method performed on Xanthorrhizol with the PCAF HAT A chain did not indicate the presence of hydrogen bonds in either the A or the B chains, due to absence of amino acid residues involved in the binding of acetyl-CoA by PCAF histone acetyltransferase. However, residues involved in hydrophobic bonds in PCAF HAT were residues that have acetyl-CoA binding functions, including Gly586, Tyr616, Cys574, Phe617, Val572, Asp610 and Ala613. Other residues in hydrophobic bonds involved were Gly586, Tyr616, Cys574, Phe617, Val572, Asp610, Ala613 and Phe573, which were residues involved in the binding of acetyl-CoA by HAT PCAF (Clements *et al.* 1999). These results suggested that Xanthorrhizol has the ability to inhibit PCAF HAT binding with acetyl-CoA in both the A and the B chains, but only hydrophobic bonds occurred. The strength of binding between A and B chains was balanced and equally strong.

These results showed that components in *C. xanthorrhiza* are highly potential in inhibiting PCAF HAT, and therefore, can inhibit tumor growth and can be used as an anti-cancer candidate. This is in line with research conducted by Bimonte *et al.* (2015), Balasubramanyam *et al.* (2004), Sandur *et al.* (2007) and Huang *et al.* (1995) that *C. xanthorrhiza* components (curcumin, demethoxycurcumin, bismethoxycurcumin and Xanthaorrhizol) may inhibit tumor growth.

CONCLUSION

Docking results on the fourth ligand components *C. xanthorrhiza* indicated that the components in *C. xanthorrhiza* are able to inhibit the binding of acetyl-CoA and histone. These results can be used to predict the inhibitory mechanism conducted by the components of *C. xanthorrhiza*. The binding residues involved in the binding of acetyl-CoA demonstrated the non-competitive ability of components in *C. xanthorrhiza* in inhibiting the PCAF HAT. The binding with PCAF HAT still allow histone to bind to the enzyme to produce complex enzyme-substrate-inhibitor having non-competitive inhibitor properties. The binding residues involved in the binding of histone demonstrated the ability of components in *C. xanthorrhiza* to inhibit the PCAF HAT on a competitive basis. Components in *C. xanthorrhiza* arguably to resemble the substrate (histone), hindering the binding to the enzyme to form a product.

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REFERENCES

Alavijeh MS, Chisthy M, Qaiser MZ, Palmer AM. 2005. Drug metabolism and pharmacokinetics, the blood-brain barrier, and central nervous system drug discovery. NeuroRx 2: 554-71.

Balasubramanyam K, Varier RA, Altaf M, Swaminathan V, Siddappa NB, Ranga U, Kundu TK. 2004. Cucurmin, a novel p300/CREB-binding protein-specific inhibitor of acetyltransferase, repress the acetylation of histone/nonhistone proteins and histoneacetyltransferase-dependant chromatin transcription. J Biol Chem 281: 40292-301.

Bimonte S, Barbecri A, Palma G, Rea D, Luciano A, D'Aluto M, Arra C, Izzo F. 2015. Dissecting the role of curcumin in tumor growth and angiogenesis in mouse model of human breast cancer. Biomed Res Int'l. ID878134. 7 p.

Chattopadhyay I, Biswas K, Bandyopadhyay U, Banerjee RK. 2004. Turmeric and curcumin: Biological actions and medicinal applications. Current Sci 87: 44-53.

Cheah YH, Azimahtol HL, Abdullah NR. 2006. Xanthorrhizol exhibits anti-proliferative activity on MCF-7 breast cancer cells via apoptosis induction. Anticancer Res 26: 4527-34.

Clements A, Rojas JR, Trievel RC, Wang L, Berger SL, Marmorstein R. 1999. Crystal structure of the histone acetyltransferase domain of the human PCAF transcriptional regulator bound to coenzyme A. EMBO 18: 3521-32.

Dekker FJ, Haisma HJ. 2009. Histone acetyltransferase as emerging drug target. Drug Discov Today 14: 942-8.

Dekker FJ, Ghizzoni M, Meer NVD, Wisastra R, Haisma HJ. 2009. Inhibition of the PCAF histone acetyl transferase and cell proliferation by isothiazolones. Bioorg Med Chem 17: 460-6.

Edwards MP, Price DA. 2010. Role of physicochemical properties and ligand lipophilicity efficiency in addressing drug safety risks. Annu Report Med Chem 45: 381-91.

Fan-Qi Z, Shi-Ming P, Li LLM, Zhen-Hua Z, Zhi-Yuan Z, Niu H. 2013. Structure based identification of drug-like inhibitors of p300 histone acetyltransferase. Acta Pharm Sinica 48: 700-8.

Ghizzoni M, Boltjes A, Graaf CD, Haisma HJ, Dekker FJ. 2010. Improved inhibition of the histone acetyltransferase PCAF by an anacardic acid derivative. Bioorg Med Chem 18: 5826-34.

Gupta S, Prasad S, Kim JH, Patchva S, Webbb LJ, Priyadarsini IK, Aggarwal BB. 2011. Multitargeting by curcumin as revealed by molecular interaction studies. Nat Prod Rep 28: 1937-55.

Hasan AEZ, Mangunwidjaja D, Sunarti TC, Suparno O, Setiyono A. 2016. Antibreast cancer activity of nanopropolis Indonesia on induced mammary gland tumor by DMBA in virgin sprague-dawley rats. BIOTROPIA 23(1): 35-41.

Huang ZJ, Curtin KD, Rosbash M. 1995. PER protein interactions and temperature compensation of a circadian clock in Drosophila. Sci 267: 1169-72.

Jantan I, Saputri FC, Qaisar MN, Buang F. 2012. Correlation between chemical composition of *Curcuma domestica* and *Curcuma xanthorrhiza* and their anti-oxidant effect on human low-density lipoprotein oxidation. Evidence-Based Compl Alternative Med 438356: 1-10.

Joe B, Vijaykumar M, Lokesh BR. 2004. Biological properties of curcumin-cellular and molecular mechanisms of action. Crit Rev Food Sci Nutr 44(2): 97-111.

Lipinski CA, Lombardo F, Segawa T, Ko D. 2001. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development setting. Adv Drug Deliv Rev 46: 3-26.

Love IM, Sekaric P, Shi D, Grossman SR, Androphy EJ. 2012. The histone acetyltransferase PCAF regulates p21 transcription through stress-induced acetylation of histone H3. Cell Cycle 11(13): 2458-66.

Mannhold R, Poda GI, Ostermann C, Tetko IV. 2007. Calculation of molecular lipophilicity: State of the art and comparison of log P methods on more than 96000 compounds. J Pharm Sci 98: 861-93.

Martz E. 2003. Introduction to bioinformatics. HAT trick: p300, Small molecule, inhibitor. Chem Biol 17: 417-8.

Monika G, Punam G, Sarbjot S, Gupta GD. 2010. An overview on molecular docking. Int J Drug Dev Res 2: 219-31.

Pérez S, Tvaroška I. 2014. Carbohydrate-protein interactions: molecular modeling insights. Adv Carbohydr Chem Biochem 71: 9-136.

Ropero S, Esteller M. 2007. The role of histone deacetylases (HDACs) in human cancer. Mol Oncology 1: 19-25.

Sandur SK, Pandey MK, Sung B, Ahn KS, Murakami A, Sethi G, Limtrakul P, Badmaev V, Aggarwal BB.

2007. Curcumin, demethoxycurcumin, bismethoxycurcumin, tetrahydrocurcumin and termerones differentially regulate anti-inflammatory and anti-proliferative responses through a ROS-independent mechanism. Carcin 28: 1765-73.

Salleh NAM, Ismail S, Halim MRA. 2016. Effects of *Curcuma xanthorrhiza* extracts and their constituents on phase II drug-metabolizing enzymes activity. Pharmacognosy Res 8: 309-15.

Sharma NK, Jha KK, Priyanka 2010. Molecular docking: An overview. J Adv Sci Res 1: 67-72.

Shiau AK, Barstad D, Loria PM, Cheng L, Kushner PJ, Agard DA, Greene GL. 1998. The structural basis of estrogen receptor/coactivator recognition and the antagonism of this interaction by tamoxifen. Cell 95(7): 927-37.

Vinsentricia A. 2015. Kinetika inhibisi dan analisis *in silico* molekuler kurkumin kunyit (*Curcuma longa*) terhadap histon asetiltransferase. [Thesis]. Bogor (ID): Institut Pertanian Bogor.

Wapenaar H, Dekker FJ. 2016. Histone acetyltransferases: Challenges in targeting bi-substrate enzymes. Clin Epigenet 8: 1-11.