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Virtual screening of compounds from the patchouli oil of *Pogostemon herba* for COX-1 inhibition

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Abstract:
Our interest is to identify compounds from the patchouli oil of *Pogostemon herba* to inhibit the cyclooxygenase-1 (COX-1) enzyme activity. The data for the major compounds (*alpha-patchouli alcohol* isomer (CD521903, CD442384, and/or CD6432585), *alpha-bulnusene, seychellene* and *alpha-guaiene)* of patchouli oil were explored from the PubChem database. The compounds to COX-1 interactions were studied using the molecular docking tools Hex 6.12 and LeadIT2 Bisolve. The interactions were further visualized using the Chimera 1.7s viewer software tool. The analysis of the major compounds of patchouli oil showed that *alpha-Patchouli alcohol* (CD521903) binds to COX-1 at many active sites including: Leu223B, Asp228B, Leu237B, Arg332B, Trp138A, Glu139A, Ser142A, and Asn143A. Further analysis revealed that these binding sites are maintained by hydrogen bonds with Ser142A, Glu139A, and Asp228B. The interaction energy between COX-1 and *alpha-patchouli alcohol* (CD521903) is -6 kJ/mol (without solvent) and -15 kJ/ mol (with solvent DMSO). These theoretical data suggests *alpha-patchouli alcohol* as a potential inhibitor of the COX-1 enzyme. However, these observations should be investigated and confirmed using experimental evidence.

Keywords: alpha-patchouli alcohol, cyclooxgenase-1, inhibitor, the major compounds of patchouli oil, *virtual screening.*

Background:
Cyclooxygenase (COX-1/COX-2) iso-enzymes were on the pathways of prostanoids: prostaglandin and thromboxane/ prostacyclin. COX-1/ COX-2 always occur as PGI2 and TXA2 to balance the thrombogenic factors in protective mechanisms during normal hemostasis **[1, 2].** COX-1/ COX-2 isoenzyme acts downstream of the enzyme *prostacyclin synthase* (PGIS) and *thromboxane synthase* (TXS) in catalyzing the synthesis of PGI2 and TXA2 **[1, 3, 4].** Vascular prostanoids opposing effects and PGI2 as vasodilators are active during thrombosis. This condition will activate platelets and promote platelet aggregation. Thus, there is always a need for an effective inhibitor of COX-1/COX-2.

Patchouli oil was traditionally obtained using steam distillation of *Pogostemon Herba* **[5].** The known compounds of patchouli oil were *alpha-patchouli alcohol*, *alpha-bulnusene, alfa-guaiene and seychellen* **[5].** Our interest is to evaluate the potential binding of these compounds with COX-1 using computational docking techniques in quantitative structure activity study (QSAR). The major compounds of patchouli oil compounds show activity of inhibitors of enzymes and nuclear receptors ligands **[6].** Therefore, we screened these compounds from patchouli oil using their structures from the *pubchem* database using the docking techniques with COX-1 followed by visualization of their molecular level interactions.

Methodology:
COX-1 sequence
The amino acid sequence of cyclooxgenase-1 (COX-1) with ID: NP_000953.2 was obtained from the sequence database of NCBI **[7].** The model of cyclooxgenase-1 (PGH1_human) was obtained from the SWISS-MODEL repository **[8].** This research protocols were approved by the Medical Ethic Committee of Brawijaya University as National Ethic Committee.

Ligand preparation

We downloaded the major compound structures of patchouli oil from NCBI PubChem. The ID of *alpha-patchouli* isomer: includes CD521903, CD442384, and CD6432585, *alpha-bulnusene*: CD94275, *seychellen*: CD519743, and *alpha-guaiene*: CD107152 **[9].** Their energy forms were minimized and converted to PDB format by Open Babel 2.3.1 in Hex.6.12 as ligands for virtual screening.

Docking ligand – protein

We used the Hex 6.12 (rigid docking) tool to compute possible interaction COX-1 with alpha-patchouli alcohol (CD_521903) at the interaction site. Output of rigid docking was refined using the portable InteLigand-LigandScout Software 2.02 and the LeadIT2 software. InteLigand-LigandScout is applied for the identification of van der Walls (vdW) interactions.

LeadIT2 software is used to simulate the most possible native complex structure of alpha-patchouli alcohol-COX-1 in flexible mode with both backbone and side-chains movements. Thereafter, we used LeadIT2 to refine the candidate models according to an energy function followed by the hydrogen bond calculations and analysis.

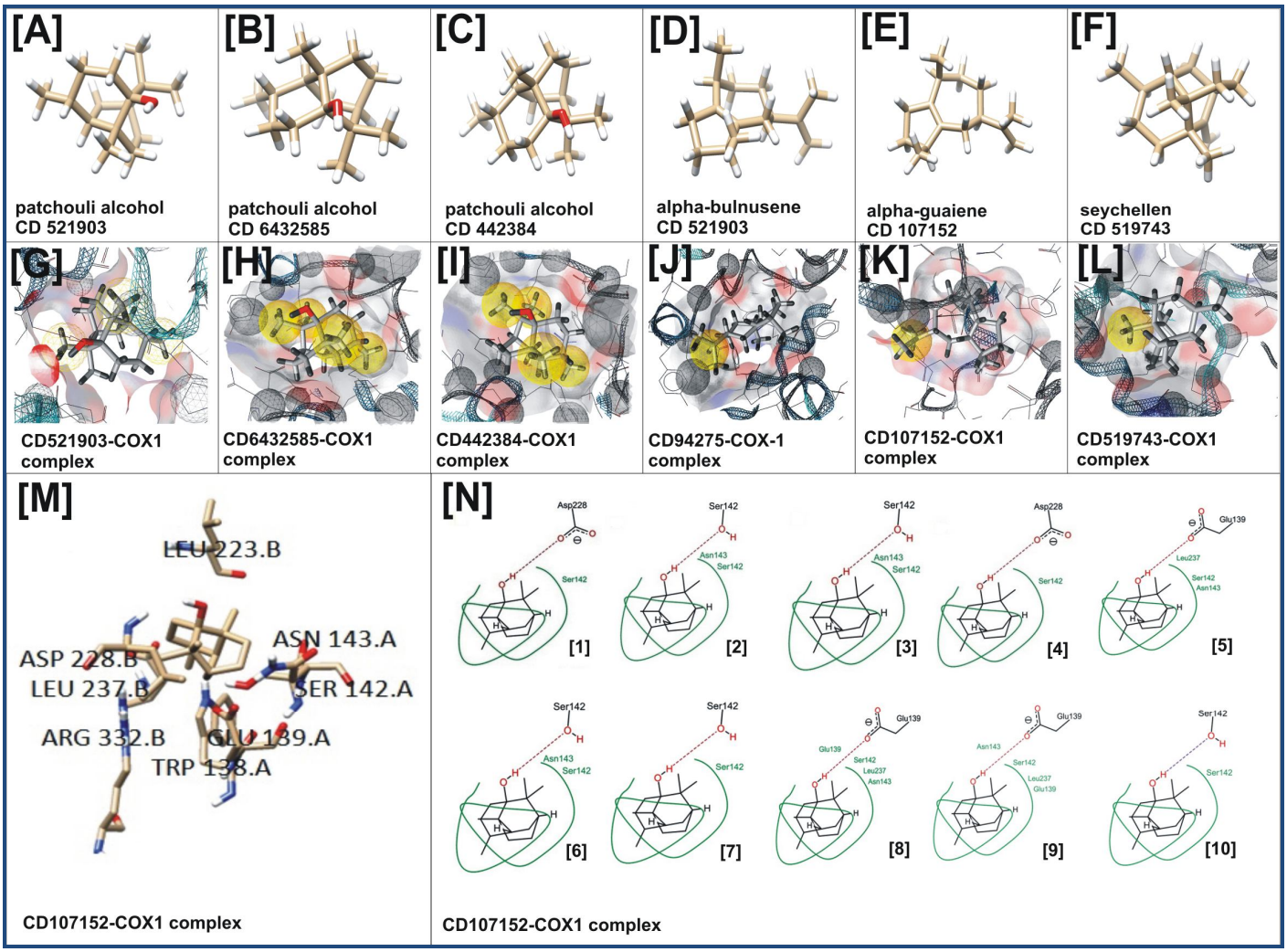

Figure 1: Modeling analyses show that alpha-patchouli alcohol (CD 521903) binds to cyclooxygenase-1 at many active sites including: Leu223B, Asp228B, Leu237B, Arg332B, Trp138A, Glu139A, Ser142A, and Asn143A. The analyses show that the alpha-patchouli alcohol (CD521903) binds to cyclooxygenase-1 by hydrogen bonds with Ser142A, Glu139A, and Asp228B. Figures in panels [A-F] show the 3D structures of alpha-patchouli alcohol isomer (CD521903, CD6432585 and CD442384), alpha-bulnusene (CD94275), alpha-guaiene (CD107152), and seychellen (CD519743) **[8].** van der Waals (vdW) patches in CD 521903-COX-1 [panel G] complex is shown with three yellow globes, [panel H] CD6432585-COX-1 and [panel I] CD 521903-COX-1 complexes with four yellow globes, [J-L] CD94275-COX-1, CD107152-COX-1, and CD519743-COX-1 complexes with one yellow globe using portable LigandScout Software (version 2.02). Modeling 3D analyses (panel M) using Hex 6.12 docking software and visualized using Chemira 1.7 viewer software show that alpha-patchouli alcohol (CD 521903) binds to cyclooxygenase-1. 2D hydrogen bond and energy analysis of CD 521903-COX-1 complex (panel N) using LeadIt 2.1.3 docking and viewer software is shown.

Visualization

Visualization of the structures was performed using the Chemira version 1.7 molecular graphics system.

Discussion:

The major known compounds of patchouli oil were *alpha-patchouli alcohol, alpha-bulnusene, seychellene and alfa-guaiene*. The

other compounds of patchouli oil were *alpha-patchoulene, alpha-gurjunene, beta-caryophylene, gemacrene-D, gemacrene-A, and viridiflorol*. The 3D structures of all compounds are available in the form file.sdf **[9].** Thereafter file.sdf is converted into file.pdb by Openbabel software and model viewing was performed using the chemira 1.7s software, as shown in (**Figure 1(A-F).** We used molinspiration analysis to report the screening of major compounds of patchouli oil, as given in **Table 1 (see supplementary material).** The result showed that major compounds of patchouli oil act as an inhibitor to protein enzymes. The amino acid sequence of target human cyclooxgenase-1 (NP_000953.2) is 93% similar to a swiss model sequence (PGH1_human) in the database. Thus, the corresponding homology model was downloaded for the docking study.

The use of structural models for ligand scanning, ligand docking and ligand activity profiling studies has been documented **[10].** Molecular model data shown in **Figure 1M** suggests that *alpha-Patchouli alcohol* (CD521903) binds to cyclooxgenase-1 at many active sites including: Trp138.A, Glu139.A, Ser142.A, Leu223.B, Asp228B, Leu237.B and Arg332.B. The output of rigid docking was further refined using portable LigandScout software (version 2.02) and LeadIT2 software. Intel LigandScout was used to identify van der Wall (vdW) interactions in the model complexes. The van der Walls (vdW) interaction analysis **(Figure 1(G-L))** confirmed three interactions of alpha-patchouli alcohol (CD521903) with COX-1.

The other major compounds of patchouli oil such as *alpha-patchouli alcohol* (CD442384 and CD6432585) have four vdW interactions and *seychellene*, *alpha-guaiene* and *alpha-bulnusene* are only one vdW interaction. Further analysis using the LeadIT software explain that *alpha patchouli alcohol* CD521903 have ten interacting hydrogen bonds with COX-1 with Ser142A, Glu139A, and Asp228B as shown in **Figure 1N**. Thus, the modeling analyses of *alpha-patchouli alcohol* (CD521903) provide better binding activity than the other compounds of patchouli oil.

The best model ligand-protein complex was further simulated for the stability of the binding interaction with and without DMSO (*dimethyl sulfoxide*) solvent. The simulation described that the addition of DMSO solvent interrupted the stability of *alpha-patchouli alcohol* (CD521903)-COX-1 interaction complex. This is an indication for the increased binding energy in the CD521903-COX-1 model complex. However, a better root mean square deviations (RMSD) of the protein complexes were observed with added DMSO solvent **Table 2 (see supplementary material).** We observed that the energies of interaction are -6 kJ/ mol (without solvent) and -15 kJ/ mol (with solvent DMSO) using the LeadIT software. These data suggest that DMSO solvent have potency to abrogate *alpha-patchouli alcohol* (CD529013)-COX-1 interaction. Molecular model data suggests that *alpha-Patchouli alcohol* as a potential inhibitor of COX-1 pending further experimental verification.

Conclusion:

The modeling analyses of major compounds in patchouli oil suggest that *alpha-Patchouli alcohol* (CD521903) binds to cyclooxygenase-1 at many active sites including: Leu223B, Asp228B, Leu237B, Arg332B, Trp138A, Glu139A, Ser142A, and Asn143A. Further analysis revealed that several of these binding sites are maintained by hydrogen bonds with Ser142A, Glu139A, and Asp228. The ligand-protein interaction energy is favorable with values of -6 kJ/ mol (without solvent) and -15 kJ/ mol (with solvent DMSO). Thus, these theoretical data suggests *alpha-Patchouli alcohol* as a potential inhibitor of COX-1 pending experimental verification for further interpretation and conclusion.

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Supplementary material:

Table 1: Physical-chemical properties of major compounds of patchouli oil

Description	a-Patchouli alcohol CID 521903	a-Patchouli alcohol CID 442384	a-Patchouli alcohol CID 6432585	a-Bulnusene CID 94275	a-Guaiene CID 107152	Seychellene CID 519743
Molecular Weight	222.36	222.36	222.36	204.35	204.35	204.35
Kinase inhibitor	-0.88	-0.88	-0.88	-1.33	-1.33	-1.30
Nuclear receptor inhibitor	0.55	0.55	0.55	0.19	0.19	0.27
Protease inhibitor	-0.32	-0.32	-0.32	-0.60	-0.60	-0.50
Enzyme inhibitor	0.40	0.40	0.40	0.07	0.07	0.28
XLogP3-AA	4.10	4.10	4.10	4.60	4.60	5.10
H-Bond Donor	1	1	1	0	0	0
H-Bond Acceptor	1	1	1	0	0	0

Source : calculated by molinspiration, 2013

Table 2: The stability of a-patchouli alcohol (CD529013)-COX-1 complex. RMSD of the CD521903-COX-1 complexes have changed significantly after added with DMSO solvent. We used Lead It software to perform energy analyses.

(A)	Without Solvent										
No.	**Posename**	**Rank**	**Score**	**Match**	**Lipo**	**Ambig**	**Clash**	**Rot**	**RMSD**	**Simil**	**Match**
1	521903_01	1	0.9236	-4.7000	-0.9614	-1.2049	0.9899	1.4000	186.2964	184.8628	1
2	521903_02	2	0.9592	-4.7000	-0.7336	-1.5623	2.1551	1.4000	186.6045	185.1544	1
3	521903_03	3	0.9708	-4.7000	-1.9513	-1.539	2.4161	1.4000	186.6822	185.2313	1
4	521903_04	4	1.0977	-4.7000	-0.9882	-1.1698	1.1557	1.4000	186.2996	184.8662	1
5	521903_05	5	1.6437	-4.3402	-3.8306	-3.0605	6.0750	1.4000	184.7433	183.2931	1
6	521903_06	6	1.7268	-4.7000	-1.7792	-1.5086	2.9146	1.4000	186.7428	185.2923	1
7	521903_07	7	2.0937	-4.7000	-1.3559	-1.0465	2.3961	1.4000	186.8906	185.4413	1
8	521903_08	8	2.1166	-4.3402	-3.4510	-2.7095	5.8173	1.4000	184.7581	183.3077	1
9	521903_09	9	2.4409	-4.3402	-2.6581	-3.0818	5.7209	1.4000	184.4859	183.0353	1
10	521903_010	10	4.8892	-1.3998	-1.4838	-1.7494	2.7222	1.4000	186.2615	184.8261	1
(B)	**With DMSO Solvent**										
1	521903_01	1	-3.3327	-4.3414	-5.5996	-3.7417	3.5500	1.4000	185.2996	183.8523	1
2	521903_02	2	-0.8694	-4.7000	-5.1680	-3.1342	5.3328	1.4000	185.3832	183.9258	1

Source: calculated by LeadIT Software, 2013