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Original Research Article

1,8-cineole in Java cardamom essential oil selectively inhibits orexin receptors (OX1R/OX2R): Molecular docking and dynamics

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Abstract

Purpose: *To determine the insomnia therapeutic potential of compounds contained in Java cardamom essential oil (JCEO) by targeting orexin-1/2 (OX-1/OX-2) receptors using molecular docking and dynamics.*
Methods: *Forty compounds from GC-MS analysis of Java cardamom essential oil were retrieved from the database, docked with orexin-1 and 2 receptors, and their interactions analyzed. Molecular dynamics simulations were carried out to study the inhibitor binding interactions of the compounds with the best docking score using OpenMM in Google Colab.*
Results: *Java cardamom essential oil compounds are bound to the sites where native ligands bind on orexin-1 (OX-1) and orexin-2 (OX-2) receptors. The binding affinity of JCEO compounds tends to be relatively selective towards orexin-2 (OX2R). 1,8-cineole is the best in its selectivity towards orexin-2 and the most stable.*
Conclusion: *1,8-cineole in JCEO could treat insomnia through selective inhibition of OX2R.*

Keywords: *Insomnia, Java cardamom essential oil, 1.8-cineol, Orexin-1/2 receptor*

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INTRODUCTION

Insomnia is a common sleep disorder characterized by persistent difficulty in falling asleep, staying asleep, or waking up too early, which leads to impaired functioning during the day. Insomnia is classified as either acute or chronic, with chronic insomnia defined as symptoms occurring at least three times per week for a minimum of three months. This condition is frequently associated with various medical and psychiatric disorders and results in significant fatigue, cognitive impairment, and mood disturbances. Moreover, individuals with insomnia are at a higher risk of developing hypertension, diabetes, depression, anxiety, substance use disorders, and even suicidal tendencies [1].

Diagnosis of insomnia often utilizes assessment tools such as the Insomnia Severity Index and the Pittsburgh Sleep Quality Index. Treatment options range from pharmacological interventions to non-pharmacological approaches, with

cognitive behavioral therapy for insomnia (CBT-I) widely recommended as an effective non-drug therapy. Early detection and management are crucial due to the considerable negative impact of insomnia on overall health and quality of life [2].

Pharmacological treatments for insomnia, though effective, may cause adverse physiological effects, especially with long-term use. Consequently, many individuals seek alternative therapies, including herbal remedies. Studies on the efficacy of herbal treatments has yielded mixed results. Herbs such as valerian, chamomile, kava, and wuling have been studied, but their effectiveness compared to placebos or conventional treatments remains uncertain [3]. More recent studies has identified *Matricaria chamomilla, Valeriana officinalis, Viola odorata,* and *Passiflora incarnata* may offer benefits by targeting the GABA system, potentially improving sleep latency and duration. Combinations of herbs, like valerian, passion flower, and hops, have also shown promise. Additionally, certain spices and rhizomes, such as ginger and *Ocimum sanctum*, have demonstrated anxiolytic and neuroprotective effects [4].

Cardamom, a member of the Zingiberaceae family, is another herb with a long history of medicinal use. In Indonesia, two main types are recognized: sabrang cardamom (*Elettaria cardamomum*) and Java cardamom (*Amomum compactum*), the latter being native to Indonesia [5]. Cardamom has been traditionally used to treat ailments such as asthma, digestive issues, and infections. Scientific studies have identified various bioactive compounds in cardamom essential oil, such as 1,8-cineole, α-terpinyl acetate, and linalool [6], which contribute to its pharmacological properties, including antibacterial, antioxidant, and anti-inflammatory effects. Studies on Java Cardamom Essential Oil (JCEO) aims to evaluate its potential in treating insomnia, particularly through orexin inhibition [7]. Different cardamom simplicia varieties in different locations have different essential oil content and therapeutic activities when extracted with different solvents (ethanol and ethyl acetate) [8]. This study evaluates the GC-MS profiling of Java Cardamom Essential Oil (JCEO) and the potency of its bioactive compounds in treating insomnia through orexin inhibition [9].

EXPERIMENTAL

Preparation of Java cardamom essential oil

Java cardamom fruit simplicia (*Amomi Compacti Fructus*) was processed into powder. The essential oil was prepared from 250 g of distilled Java cardamom powder by steam distillation. The oil was extracted with n-hexane and purified by evaporating n-hexane [8].

Gas chromatography and mass spectrometry of Java Cardamom Essential Oil

Java cardamom essential oil was analyzed by gas chromatography-mass spectrometry (GC-MS QP2010 Plus) with column static phase nonpolar/polar. The oil was passed through Agilent 19091S-433 HP-5MS. The column temperature was initially set and then gradually increased by 10 °C, over 28 min, until reaching a final temperature of 288 °C. The chemical constituents were detected with mass spectrometry (MS).

Receptors and ligands retrieval

Interactions of Java cardamom essential oil compounds with orexin receptors were virtually analyzed by molecular docking and dynamics on receptors OX1R (4ZJ8) and OX2R (7XRR) [9] These were obtained from RCSB PDB. Receptors were prepared by removing water and native ligands. Hydrogen ions were added later to the receptors by AutoDock Tools [10]. The 3D structures of selected 30 ligands were downloaded as an SDF file from PubChem (Table 1), converted to PDB file, and energy minimization was done with Avogadro 1.2.0.

Molecular docking and dynamics

Molecular docking was performed in Autodock Vina 1.2.3. Docking of ligands to receptors was performed in the grid box optimized by the program [10]. The gridbox was also validated by re-docking with the native ligand of each receptor. The 2D and 3D results were visualized in Discovery Studio. Molecular dynamics simulations were carried out to study the inhibitor binding interactions of compounds with the best docking score, (1.8-cineole) with OX1R (4ZJ8) and OX2R (7XRR) receptors. The interaction uses OpenMM in Google Colab. Three-dimensional structures of 1.8-cineole were obtained from the PubChem Open Chemistry Database. Three structures of various compounds in smile format are then converted into *.pdb files using LigParGen, a web-based service that provides force field (FF) parameters for organic molecules or ligands. To set the environment for MD calculation, all necessary libraries and packages were installed for the simulation. The main packages installed were: Anaconda, OpenMM, PyTraj, py3Dmol, ProLIF, Numpy), Matplotlib, and AmberTools.

Ligand and protein *.pdf files were uploaded and diversified on g-drive and g-colab. Molecular dynamics simulations were carried out systematically following the steps set out by OpenMM in Google Colab. The parameters to generate the protein topology are force field: FF19sb; water type: TIP3P; the concentration in Molar units, AMBER tleap will neutralize the system ion: 0.15M NaCl. The parameter to generate the ligand topology is ligand Force field: GAFF2. The parameters for MD equilibration protocol are: Minimization steps 1,000; simulation time 5 nanoseconds and integration time 2 femtoseconds, temperature 310K, pressure 1 bar, frequency to write the trajectory file (10 picoseconds), and frequency to write the log file (10 picoseconds). Running a production MD simulation: simulation time (10 nanoseconds), number of strides (1 integers) and integration timestep (2 femtoseconds). The interaction energy and solvation free energy for the complex, receptor and ligand were calculated and the average was taken to estimate the binding free energy. The binding energy was calculated using both the MM-GBSA method and the MM-PBSA method for comparison. GB/SA input parameters are the OBC models, igb=2 and salt concentration 0.15. The LigPlot before and after simulation, interaction energy, the distance between the ligand and catalytic site residues, the distance between the ligand and specific residues, RMSD of protein's CA atoms were computed, and RMSD was plotted as a distribution, RMSF of protein's CA atoms, and other analyses were determined [11].

RESULTS

Phytochemical constituents of Java cardamom essential oil

A total of 40 phytochemicals were detected in the Java cardamom essential oil (Figure 1; Table 1). The phytochemical constituents were classified into two groups of secondary metabolites, sesquiterpenoids and monoterpenoids.

Binding affinity of Java cardamom essential oil compounds to orexin receptors

The selective binding of Java cardamom essential oil compounds to orexin receptors was screened through binding affinity scores. The binding of those compounds was compared with that of lemborexant and suvorexant as controls. Java cardamom essential oil bioactive compounds bound to orexin receptors in a mild, selective manner (Table 2).

Molecular docking interaction of Java cardamom essential oil compounds with orexin receptors

According to the binding affinity and binding selectivity, 1,8-cineole was the most potent OXs inhibitor. The interactions of 1,8-cineole with OX1R and OX2R were further examined in the 3D visualization (Figure 3 a and b). The interaction of OX1R with 1,8-cineole was facilitated through alkyl bond: Lys A:241, and van der Waals forces: Ile A:148, Leu A:242, Arg A:243, Met A:245, Met A:290, Arg A:293, Asp A:1148, and Phe A:1195 residues.

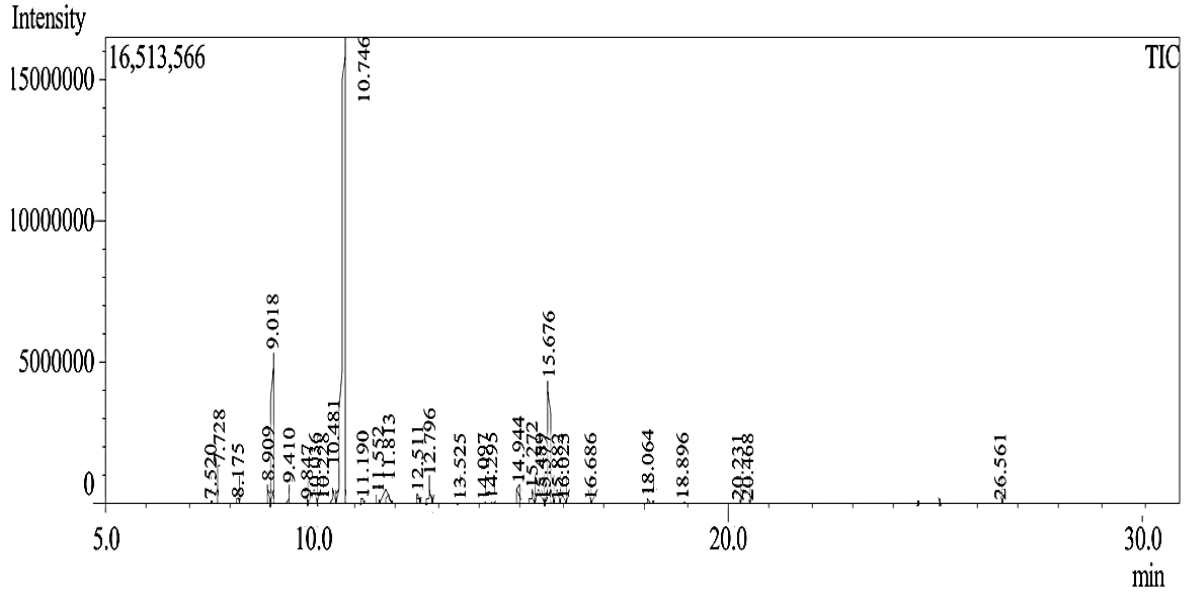


Figure 1: TIC Java Cardamom Essential Oil Compounds using GC-MS QP2010 Plus analysis

Table 1: GC-MS analysis of Java cardamom essential oil

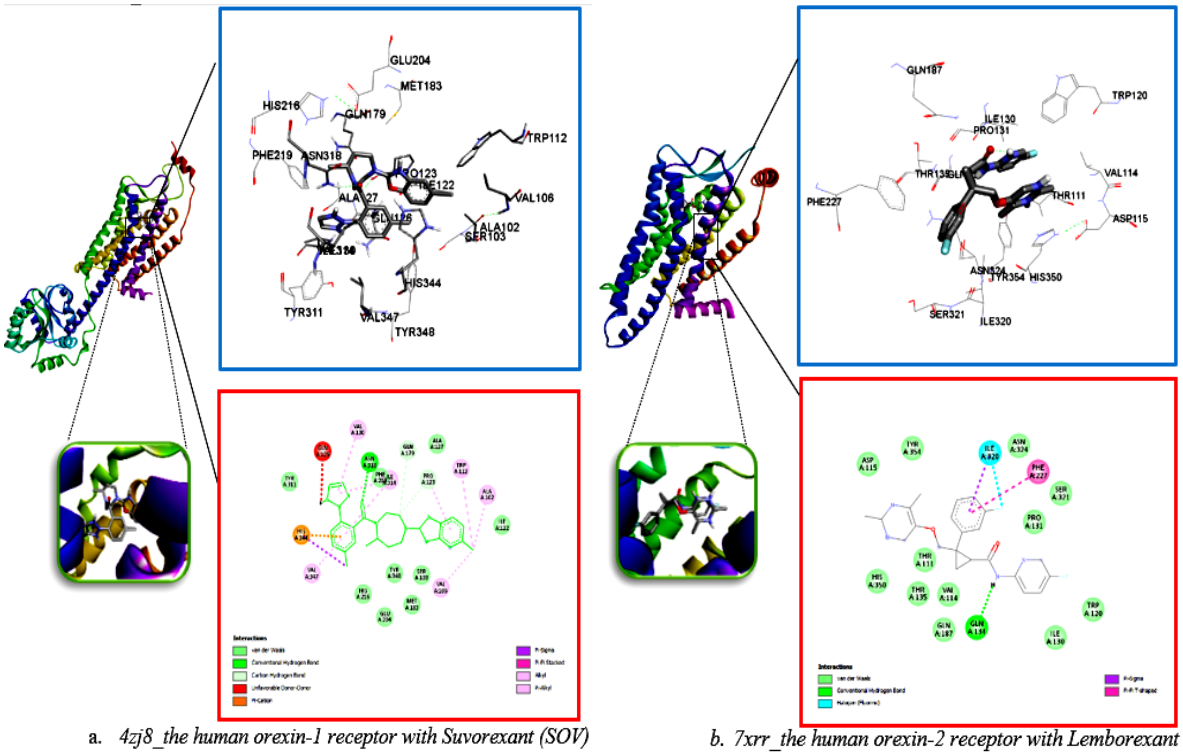
No.	RT (min)	Composition (%)	CID	Compound	Type of secondary metabolite
1	10.746	63.21	CID2758	Eucalyptol/1,8-cineole	Monoterpenoid
2	9.018	10.49	CID14896	beta-Pinene	Monoterpenoid
3	15.676	9.07	CID17100	alpha-Terpineol	Monoterpenoid alcohol
4	10.481	2.75	CID10703	o-Cymene	Monoterpenoid
5	7.728	2.37	CID11051711	(+)-Sabinene	Monoterpenoid
6	12.796	1.69	CID6549	Linalool	Monoterpenoid alcohol
7	11.813	1.34	CID62367	4-Thujanol	Monoterpenoid alcohol
8	8.909	1.27	CID 68140	Pseudolimonene	Monoterpenoid
9	14.944	1.22	CID 81722	delta-Terpineol	Monoterpenoid alcohol
10	9.410	1.11	CID 31253	beta-Myrcene	Monoterpenoid
11	15.272	0.89	CID 11230	Terpinen-4-ol	Monoterpenoid
12	12.511	0.70	CID 1201521	D-Fenchone	Monoterpenoid
13	11.552	0.52	CID 7461	gamma.-Terpinene	Monoterpenoid
14	18.064	0.37	CID 637511	Cinnamaldehyde, (E)	Phenylpropanoid, Aromatic aldehyde
15	24.878	0.32	CID10104370	beta.-Bisabolene	Sesquiterpenoid
16	25.219	0.17	CID578929	(-)-.alpha.-Panasinsen	Sesquiterpenoid
17	24.485	0.29	CID 564533	Bicyclo(5.3.0)decane, 2-methylene-5-(1-methylvinyl)-8-methyl	Sesquiterpenoid
18	8.175	0.19	CID 6616	Camphene	Monoterpenoid
19	11.190	0.17	CID 18756	beta.-Ocimene	Monoterpenoid
20	14.295	0.14	CID 159055	D-Camphor	Monoterpenoid
21	24.342	0.14	CID 5317570	Germacrene D	Sesquiterpenoid
22	24.669	0.13	CID442393	beta-Selinene	Sesquiterpenoid
23	9.847	0.13	CID 7460	alpha.-Phellandrene	Monoterpenoid
24	7.520	0.11	CID 17868	alpha-thujene	Monoterpenoid
25	16.023	0.10	CID42626427	(-)-cis-Sabinol	Monoterpenoid alcohol
26	10.036	0.10	CID26049	3-Carene	Monoterpenoid
27	15.882	0.08	CID88301	(-)-Myrtenol	Monoterpenoid alcohol
28	24.407	0.08	CID10655819	gamma-Selinene	Sesquiterpenoid
29	16.686	0.07	CID 529885	exo-2-Hydroxycineole	Monoterpenoid
30	18.896	0.07	CID 10364	Carvacrol	Phenolic
31	10.228	0.07	CID 7462	alpha-Terpinene	Monoterpenoid
32	14.097	0.06	CID 102667	Pinocarveol	Monoterpenoid alcohol
33	25.089	0.06	CID6432404	(+)-gamma-cadinene	Sequiterpenoid
34	26.561	0.06	CID6428435	7-epi-cis-sesquisabinene hydrate	Sequiterpenoid
35	20.468	0.05	CID 351031	Isoascaridol	Monoterpenoid
36	15.489	0.05	CID 14529	p-Cymen-8-ol	Monoterpenoid alcohol
37	20.231	0.05	CID10655819	gamma-Selinene	Sesquiterpenoid
38	15.577	0.05	CID10931630	Isopinocarveol	Monoterpenoid alcohol
39	24.564	0.04	CID25147318	Sesquithujene	Sesquiterpenoid
40	13.525	0.04	CID 122484	p-Menth-2-en-1-ol	Monoterpenoid alcohol

Compared to suvorexant and lemborexant as controls, 1,8-cineole formed the weakest binding due to the least number of amino acid residues that comprised the complex.

Based on these results, 1,8-cineole targeted the OX1 and OX2 receptors in a different manner than suvorexant and lemborexant (Figure 2 a and b). 1,8-Cineole better interacts with OX2R through different amino acid residues than with OX1R; therefore, 1,8-cineole was deemed the best JCEO compound to inhibit human orexin-2 receptor.

Molecular dynamics simulation of 1.8-cineole-Orexin-2R complex

Molecular dynamics simulations of 1.8-cineole-OX2R complexes are shown in Figure 4 and the supplementary. However, the simulation analysis of the 1.8-cineole-OX1R interaction is very unstable, so the analysis was not described.



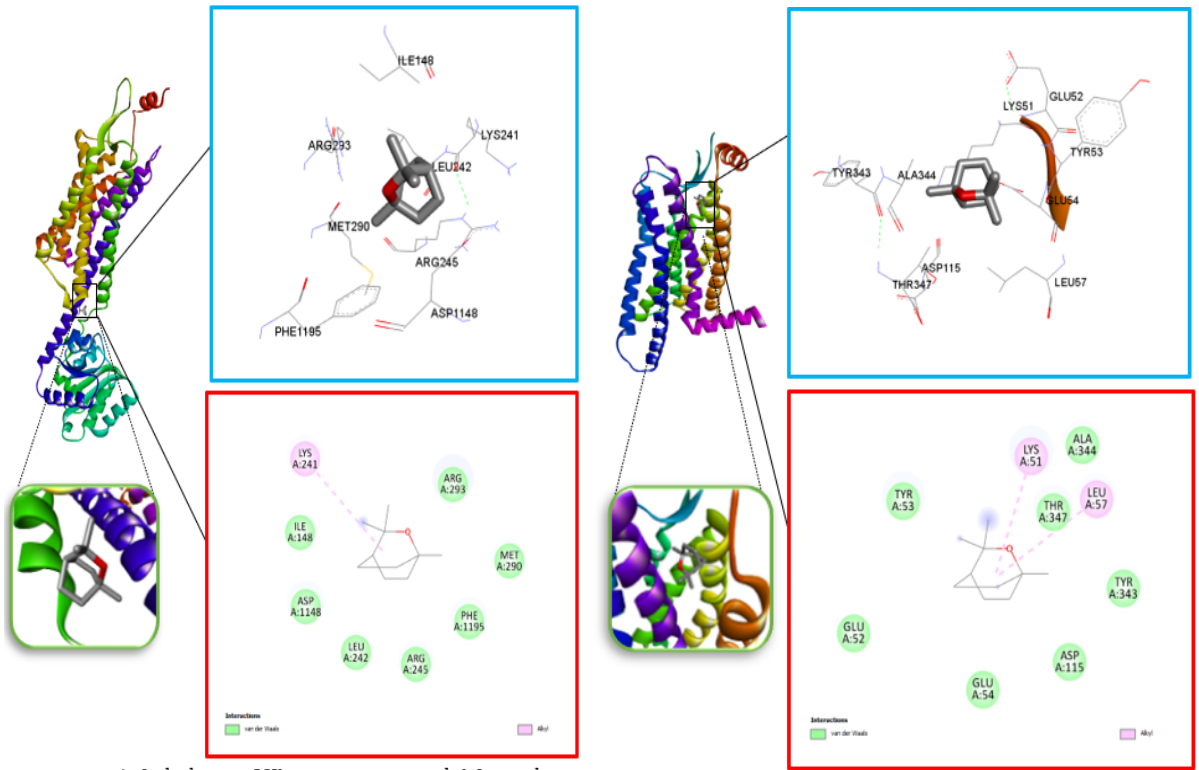
a. *4zj8_the human orexin-1 receptor with Suvorexant (SOV)*

Binding Affinity = -12.2 kcal/mol

b. *7xrr_the human orexin-2 receptor with Lemborexant*

Binding Affinity = -10.35 kcal/mol

Figure 2: Two-/Three- dimensional visualization Interaction (a) 4zj8_the human orexin-1 receptor with Suvorexant (SOV); (b) 7xrr_the human orexin-2 receptor with Lemborexant



a. *4zj8_the human OX1 orexin receptor with 1.8-cineole*

Binding Affinity = -4.893 kcal/mol

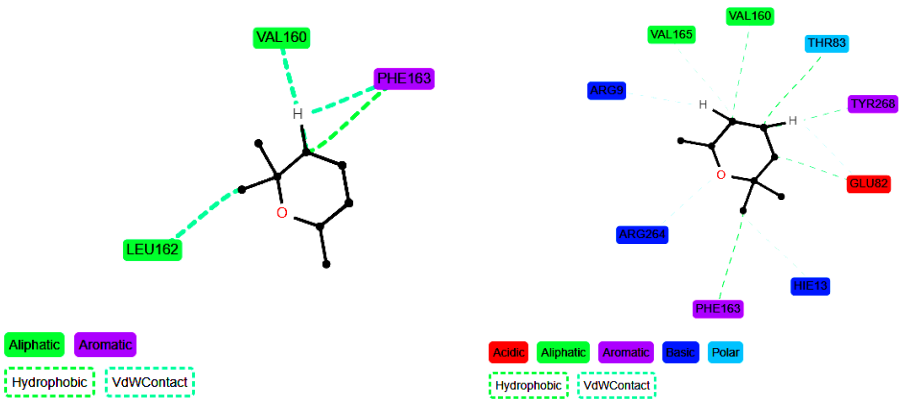
b. *7xrr_the human OX2 orexin receptor with 1.8-cineole*

Binding Affinity = -5.608 kcal/mol

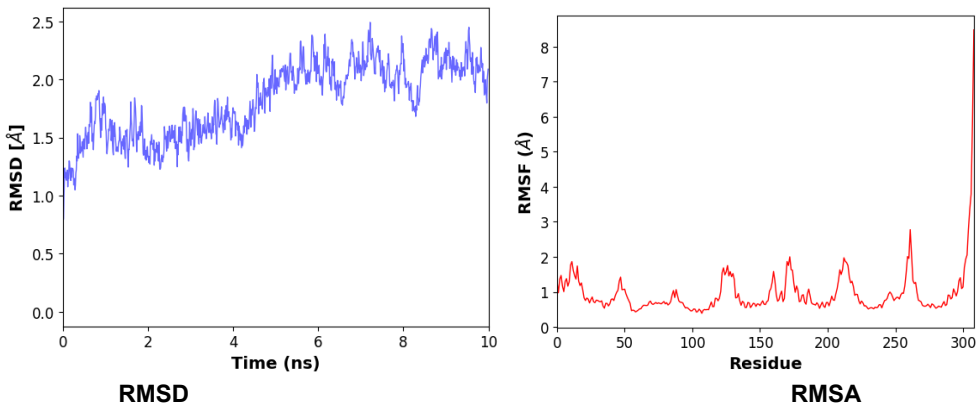
Figure 3: Two-/Three-dimensional visualization Interaction (a) 4zj8_the human orexin-1 receptor with 1.8-cineole, (d) 7xrr_the human orexin-2 receptor with 1.8-cineole

Table 2: Binding affinity of Java cardamom essential oil compounds to OX-1 and OX-2 receptors

Ligand/Compound that binds to OX-1/2 receptor	Binding Affinity (kcal/mol)		Binding selectivity
	OX1-R 4zj8_the human OX1 (Orexin-1 receptor)	OX2-R 7xrr_the human OX2R (Orexin-2 receptor)	OX1-R/OX2-R -log (BA OX2-R/OX1-R
Lemborexant (CID56944144)	-7.112	-10.35	-0.1623
Suvorexant (CID24965990)	-12.2	-0.002203	3.74335
Eucalyptol/1,8-cineol CID2758	-4.893	-5.608	**-0.05923**
beta.-Pinene CID14896	-4.557	-5.794	-0.10430
alpha.-Terpineol CID17100	-4.544	-5.880	-0.11194
o-Cymene CID10703	-4.477	-5.726	-0.10686
(+)-Sabinene CID11051711	-5.129	-5.311	-0.01514
Linalool CID6549	-4.021	-5.247	-0.11558
4-Thujanol CID62367	-4.93	-5.358	-0.03616
Pseudolimonene CID 68140	-5.244	-5.697	-0.03598
delta-Terpineol CID 81722	-5.235	-6.043	-0.06234
beta-Myrcene CID 31253	-3.875	-5.326	-0.13813
Terpinen-4-ol CID 11230	-4.652	-5.563	-0.07767
D-Fenchone CID 1201521	-4.619	-5.721	-0.09292
gamma.-Terpinene CID 7461	-4.805	-5.782	-0.08038
Cinnamaldehyde, (E)	-4.426	-5.646	-0.10573
beta.-Bisabolene CID10104370	-4.647	-5.926	-0.10559
(-)-.alpha.-Panasinsen	-5.586	-7.635	-0.13571
Bicyclo …-8-methyl CID 564533	-5.232	-7.285	**-0.14376**
Camphene CID 6616	-4.765	-5.475	-0.06032
beta.-Ocimene CID 18756	-4.681	-5.495	-0.06963
D-Camphor CID 159055	-4.481	-5.551	-0.09300



The pose and interaction pattern of 1,8-cineole in the 7xrr-OX2-R enzyme



RMSD **RMSA**

Figure 4: Molecular dynamic simulation, RMSD, and RMSA of 1.8-cineole-OX2-R complex

DISCUSSION

The GC-MS analysis of Java cardamom essential oil has revealed that 1.8-cineole was the most abundant bioactive compound with 63.21 % composition. From 40 Java cardamom essential oil bioactive compounds, 1.8-cineole selectively interacts with orexin receptors, as shown by the selectivity score of -0.05923. The binding affinity of 1.8-cineole with receptors was -4.893 kcal/mol and -5.608 kcal/mol to OX1R and OX2R, respectively. The compound was also likely to form the strongest binding to OX2R of all Java cardamom essential oil bioactive compounds, as it has the highest binding affinity with OX2R. Bicyclo(5.3.0)decane, 2-methylene-5-(1-methylvinyl)-8-methyl (CID 564533) in the Java cardamom essential oil showed the ability to interact with OX2R with the binding selectivity of -0.14376 kcal/mol.

The molecular docking of 1.8-cineole with OX2R was facilitated through alkyl bonds: Lys A:51, Leu A:57 and van der Waals interactions: Glu A:52, Tyr A:53, Glu A:54, Tyr A:343 and Thr A:347, as shown in Figure 2 d. The binding affinity of 1,8-cineole to OX1R was moderately similar to that of lemborexant to OX2R. Both ligands interacted with OX1R through alkyl bonds: Lys A:241, and van der Waals forces: Ile A:148, Leu A:242, Arg A:243, Met A:245, Met A:290, Ag A:293, Asp A:1148, and Phe A:1195 (Figure 2 c). The 1,8-cineole-OX2R complex comprised of more amino acid residues than the lemborexant-OX2R complex, indicating the potency of 1,8-cineole to inhibit OX2R at multiple sites.

The root mean square deviation (RMSD) of the protein's backbone from its initial to final conformation was used to study the stability of the protein–ligand complex. The RMSD simulation showed 1,8-cineole-OX2R complex achieved overall stability after 2 nanoseconds, with RMSD stabilizing at an average of 1.9 Å (Figure 4 b) [12]. These results indicated that the 1,8-cineol-OX2R complex was more stable during the simulation time than the other JCEO compounds. The root mean square fluctuation (RMSF) value is the fluctuation of the protein's residues from its average position throughout the simulation, representing the flexibility of the protein structure. Based on the timeline result, 1,8-cineole effectively interacted with the orexin-2 receptor binding site (Figure 4 c). 1,8-cineole interacted with the residue of the active site and the A-domain site, and reduced the fluctuations of the sites in orexin-2R. Furthermore, Figure 4a illustrates the timeline interactions of the 1.8-cineole with the active sites of orexin-2R at the simulation time. The binding energy of 1.8-cineole-orexin-2R complex using MMPBSA and MMGBSA solvent model was reported by Open MM in Google Colab. The MMPBSA binding energy (Δ G) of 1.8-cineole-orexin-2R complex is -10.5818 ± 1.9910 kcal/mol and the MMGBSA binding energy (ΔG) of 1,8-cineole-orexin-2R complex is -0.6186 ± 1.6178 kcal/mol.

The difference in the binding energy value between MMPBSA and MMGBSA could be due to polar and nonpolar contributions to ΔG, ΔT and ΔS, and the type of bonds, angles, dihedral energies, electrostatic energies and van der Waals energies [13]. Aside, the binding energy value of 1,8-cineole-OX2R complex is more stable, and this is in line with the RMSD and RMSA values. Orexin, consisting of OX1 and OX2, is are neuropeptide that regulates feeding behavior and various neuro-related mechanisms. Orexins modulate the sleep-wake cycle, neuroendocrine functions, glucose metabolism, energy homeostasis, and stress-adaptive responses; thus, investigating potential sleep-wake cycle modulators through orexin receptors is reasonable. Suvorexant and lemborexant are the popular dual orexin receptor antagonists that are often administered for treating insomnia. An earlier study has compared the potency of the natural bioactive compound in ginger, alpha-zingiberene, with commercial orexin receptor antagonist.

Virtual *in silico* analysis is a dynamic screening tool for novel therapeutic agents. *In silico* analysis was used to identify a potential orexin inhibitor by comparing the activity of alpha-zingiberene with suvorexant and lemborexant against OX1R/OX2R. The potency of ginger bioactive compounds against orexin receptors was investigated based on binding affinity and binding site. The selectivity of alpha-zingiberene to OX1R/OX2R is the highest among all identified ginger bioactive compounds. As an orexin antagonist, alpha-zingiberene likely bound OX1R/OX2R with moderately similar binding behavior as lemborexant. Alpha-zingiberene could prevent the coupling of orexins with their cognate G-protein coupled receptors (GPCRs), OX1R with Hcrtr-1 and OX2R with Hcrtr-2 [14]. Orexin antagonists allow the inhibition of phospholipase C (PLC), phospholipase A (PLA), phospholipase D (PLD), and adenylyl cyclase (AC), resulting in low cytosolic Ca^{2+} and reduced downstream cascade response [15]. Java cardamom is a famous medicinal herb known for its biological activities. Bioactive compounds of ginger have been proven for their activities in neurophysiological mechanisms and the blood-brain barrier [16]. The major constituents in

ginger, 1,8-cineole and beta-pinene, relieve migraine, protect the neurons and modulate monoamine oxidase A (MAO-A), and GABA [17].

Previously, JCEO exerted antiseizure activity in the PTZ-kindling mice model. Treatment with 6-gingerol also effectively upregulated GABA levels in the hippocampus and cortex of the senile female rats. The potency of 1,8-cineole to act as orexin antagonist via modulation of GABA, as lemborexant, was investigated [18]. Treatment with 1,8-cineole via OX1R/OX2R may increase the sleep drive and inhibit wake-promoting neurons, improving the total amount of sleep and daytime alertness. Cardamom, a natural herb, may exhibit fewer adverse effects than drugs. However, the physiological effect of 1,8-cineole remains unknown; thus, further studies are required to evaluate its potency.

CONCLUSION

This study has revealed that 1,8-cineole in Java cardamom essential oil could treat insomnia through selective inhibition of OX2R. Treatment with natural bioactive compounds could reduce adverse effects and enhance effective healing. This study has provided standardization parameters for Javanese cardamom volatile oils, which are required in developing therapies for various diseases through pre-clinical as well as future clinical trials.

DECLARATIONS

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Ethical approval

None provided.

Use of Artificial intelligence/Large language models

We also declare that we did not use Generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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