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Research Article

Molecule Attachment and Prediction of ADMET Compounds in *Cinnamomum burmannii* on Orexin Receptor as Anti-insomnia

Resmi Mustarichie*, Nyi Mekar Saptarini, Sandra Megantara

ABSTRACT

Background and Objectives: Insomnia is a sleep disorder characterized by a person's dissatisfaction with the quantity or quality of sleep. Suvorexant is a sedative and hypnotic drug that has been shown to be useful for the treatment of insomnia and can act more centrally and selectively on the orexin system. However, suvorexant has quite a lot of side effects. According to research, cinnamon has pharmacological benefits, one of which is anti-insomnia. The aimed this study to determine the interaction between the compounds contained in the cinnamon plant and the Orexin receptor with the molecular anchoring method and to determine the prediction of the ADMET properties of cinnamon compounds which have the potential as anti-insomniac. **Material and Methods:** The research method was *in-silico* study consisted of validation, bonding of cinnamon compounds and prediction of ADMET properties. **Results**: The results showed that cinnamon compounds, namely Cinnamic acid and Methylhidroxy calcone, had the best interactions with lower Gibbs bond energy values (ΔG) and inhibition constants (Ki). From the results of the prediction of ADMET properties, the Methylhydroxy calcone compound obtained positive results on the hepatotoxicity parameter and the Cinnamic acid compound obtained negative results, which means that the compound does not have toxic properties. **Conclusion:** The Cinnamic acid could be used as a new promising anti-insomnia agent.

Key words: ADMET, Cinnamic acid, *Cinnamomum burmanii*, Insomnia, Orexin.

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INTRODUCTION

Insomnia is a sleep disorder complaint, where there is difficulty in starting sleep, maintaining sleep or poor sleep quality.[1] It is estimated that 30%-50% of adults experience insomnia and 9%-12% of them experience chronic insomnia.[2] In Indonesia, about 10% of the total population or about 28 million people experience insomnia. Insomnia is often associated with the occurrence of problems in life, such as depression and anxiety.[3,4]

Insomnia can be associated with the presence of orexin, which is a neuropeptide secreted from lateral hypothalamic neurons in the brain.[5] The presence of orexin can make a person stay awake and alert, so it can trigger a person to have difficulty sleeping. Therefore, a sleep aid that targets the action of orexin is needed, namely an orexin receptor antagonist, whose work can block orexin activity in the brain. The orexin receptor antagonist that can be used is Suvorexant. Suvorexant has been approved by the US Food and Drug Administration (FDA)[6] as a new sedative and hypnotic drug that has been shown to be useful for the treatment of insomnia. Suvorexant binds to the human Orexin 1 (OX1R) and Orexin 2 (OX2R) receptors, which can inhibit orexin receptor activity.[5] This drug is thought to act more centrally and selectively on the orexin system.[7] However, chemical drugs that are often used including suvorexantt also have some side effects including headache, dry mouth, cough, respiratory tract infection, abnormal dreams, impaired memory and difficulty focusing.[8] (Lee and Parish, 2016).

Therefore, not a few insomniacs choose to use herbs as an alternative treatment, because it is believed that herbal medicines have fewer side effects. The World Health Organization (WHO) recommends the use of herbal medicines for health maintenance, prevention and treatment. It is considered safer than modern chemical drugs. Herbal medicine is believed to have fewer side effects compared to modern chemical drugs.[9] One of the herbal plants that is thought to have the potential to overcome this problem is *C. burmannii*. It is one of the many plants in Indonesia. According to Ravindran[10] cinnamon has pharmacological benefits including as an anti-oxidant, anti-tumor, anti-inflammatory, anti-viral and sedative. The sedative effect contained in cinnamon can be used for the treatment of insomnia. However, the content of specific compounds that have a sedative effect is not known.

The information from the research results of Ravindran determination of specific compounds contained in cinnamon plants that have a sedative effect can be done using the molecular anchoring method, where this method can predict the noncovalent bonds of macromolecules, namely a large molecule (receptor) and small molecule (receptor) ligands) effectively.[11] The compound contained in cinnamon is used as a ligand and the receptor is the orexin receptor. Using this method is expected to reduce the search time and also reduce costs.[12] However, in drug discovery and development, it is not enough to have sufficient efficacy against therapeutic targets, the exact properties of ADMET at therapeutic doses also need to be seen.[13] In the determination and development of drugs, there are still many drug candidates that fail to become drugs. Lack of efficacy and safety are the two main causes leading to drug failure. Therefore, ADMET plays an important role in every stage of drug discovery and

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development. Thus, it is necessary to find an efficacious molecule with better ADMET properties.[13]

Based on the description above, this study reports prediction the affinity of the compounds contained in the cinnamon plant with the best activity which is efficacious as an anti-insomniac where the results can be used as information in drug design.

MATERIALS AND METHODS

Materials

The material used in this study was a 3D structure of the compound contained in cinnamon drawn using ChemOffice 2010, orexin receptors obtained from the Online Protein Data Bank (PDB) database (http://www.rscb.org/pdb) with ID 4S0V.

Hardware and software

The hardware used was a personal computer. The software used were ChemOffice 2010 and ChemDraw Ultra 12.0 programs to draw ligand structures in 2D and 3D, Autodock 4.2 Tools program for visualization of biomolecule complexes in structure or function analysis as well as in molecular design and Biovia Discovery Visualizer 2016 program for complex visualization of pdb, the binding of the ligand to the receptor in the validation process

Research methods

The method used in this study was *in-silico* study consisted of receptor preparation, ligand preparation, program validation, molecular anchoring and interpretation of data analysis and prediction of ADMET.

Receptor preparation

The receptor used was the orexin receptor with a crystal complex shape and its ligands obtained from the protein data bank which was an online database in the form of a pdb file format with ID 4S0V. Then separated. The pdb file was still in a complex form with standard ligands, so it was separated first using the BIOVIA Discovery Studio 2016 software to also remove water molecules.

Ligand preparation

Ligand preparation was done by making a two-dimensional structure of the compound to be tested, namely the compounds contained in cinnamon using ChemDraw in 2D form, the results were saved in mole file format. Then the structure that had been obtained was converted into three-dimensional (3D) using ChemBio3D Ultra 12.0 to minimize energy and saved in .pdb format.

Program validation

After obtaining the data, validation was carried out, the results obtained were used to base the validity of a software that had been installed on a laptop to be used for molecular docking based on the Root Mean Square Deviation (RSMD) value and the results of re-docking between the ligand and receptor.

Molecular tethering simulation

Then the molecular bonding of the compounds contained in cinnamon was carried out. Grid arrangement was done so that it could cover all residues that play a role in bonding chemical compounds. Determining the grid parameters was done using AutoDock 4.2 Tools software which aimed to determine the coordinates and outer area of the active pocket of the protein.

Grid parameters

Grid parameters needed to be done in order to determine the parameters that would be used for calculations. The file format used was .gpf. The process was carried out on hardware using the Command Prompt and entering the code "autogrid 4 –p grid.gpf –l grid.glg &", after this process was done it would generate all the files that would be used for the next process.

Tethering process

In the tethering process, firstly a parameter was created with a .dpf file format. This parameter was used to determine the calculation parameters of the Lamarckian Genetic Algorithm. The process was carried out on hardware using the Command Prompt by entering the code "autogrid4 –p grid.gpf –l grid.glg &". Then automatically tethering runned and when it was finished, the results would come out.

ADMET prediction

ADMET prediction was carried out using the ADMETsar Program which was carried out on the website www.lmmd.ecust.edu.cn. Cinnamon compounds that would be predicted in the picture first then click the save sign then click the predict sign then some data from the ADMET results woul appear from the compound to be analyzed.

RESULTS AND DISCUSSION

Receptor-Ligan preparation

The first process was to search for the required receptor and ligand, both of which were obtained from the online database of the Protein Data Bank, which was a collection of biological macromolecular structural data. The orexin receptor structure was downloadable in PDB with ID 4S0V. In this ID, the receptor was still bound to the carrier ligand, so it needed to be separated using the Biovia Discovery Studio software. In anchoring the test ligand to the orexin receptor, the receptor is first separated from the ligand that binds it, namely suvorexant.

Orexin receptor active site

To be able to see the active site of the orexin receptor with (PDB code: 4S0V), it was done by visualizing the interaction between the ligand and the receptor. Visualization was carried out on the Biovia Discovery Study software by looking at the interaction of amino acid residues with suvorexant ligands so that the active site of the receptor will be known

It can be seen in Figure 1 where the visualization showed several amino acid residues that interacted with the suvorexant ligand on the active site of the receptor. The result of this interaction showed that there was hydrogen bonding through hydrogen atoms with amino acid residues of Asn324 with a distance of 2.08. Then there were -cation interactions with His350 residues, -sigma interactions with Ile320 amino acid residues, hydrogen-carbon bond interactions with Pro131, -sulfur interactions with Cys107 amino acid residues, and Alkyl and -alkyl interactions with Phe227, His224 amino acid residues. Tyr354, Val353, Val138, Ile130, Trp120, Val114 and Ala110.

Tethering validation

Validation was carried out on the separated receptor and ligand, by re-tethering the suvorexant ligand bound to the orexin receptor (PDB code: 4S0V). Parameters seen were by looking at the value of Root Mean Square Deviation (RMSD) where this value determined the success of the binding between the receptor and the ligand used. The RMSD value obtained was 0.681, from these results the value met the standard requirements for the RMSD value in the tether, which was < 2.00. The data can be seen in Table 1.

Binding compounds – cinnamon compounds with orexin receptors

Molecular tethering of compounds contained in cinnamon was carried out to find out which compounds could potentially be used as anti-

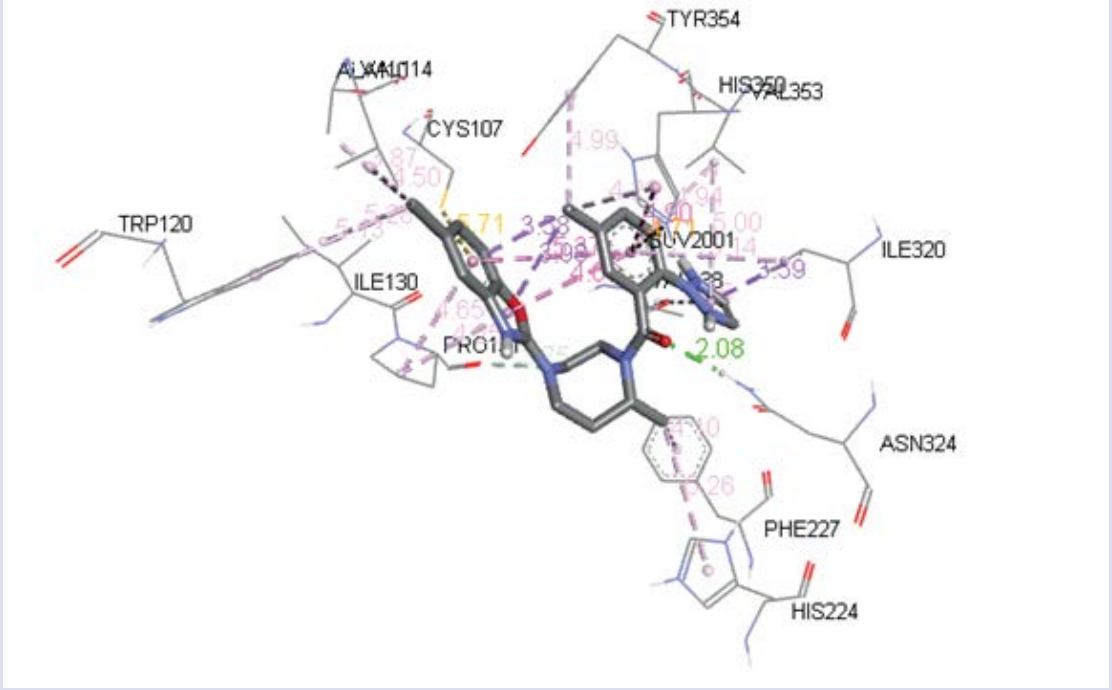

Figure 1: Interaction of suvorexant with amino acid residues.

Table 1: Validation results of suvorexant ligand re-tethering on orexin receptor active side (PDB Code: 4S0V).

Receptor	RMSD	ΔG (kcal/mol)	Ki (nM)	Amino acid residues
4S0V	0.681 Å	-9.93	52.60 nM	Ile320, Val138, Asn324, Pro131, Cys107, Ile130, Trp120, Val114, Ala110, Phe227, His224, Tyr354, His350, Val353

insomnia drugs whose mechanism was to inhibit orexin receptor activity so that there was selective inhibition of orexin receptors. The search was carried out using the *in silico* method so that it was more efficient in searching time. The process was carried out by looking for the compounds contained in cinnamon, then analyzing the interaction of the active side of the orexin receptor by tethering the molecule and then from each compound the best interaction result was seen. The structure of the compound used in this study was the structure drawn by using ChemDraw and Chembio3D. These compounds consist of 1.8 Cineole, Alpha Pinene, Alpha Terpineol, -Caryophyllene, Borneol, Cinnamic Acid, Coumarin, Champor, Cinnamyl Alcohol, Cynnamaldehyde, Eugenol, Methylhidroxy Calcone, p-Cyemene, Quercetin, Tannin and Terpinen-4 -ol. After the compounds were drawn, then the energy of the compounds was minimized first so that during the tethering process, the energy used when attaching the receptor and ligand was the result of the minimum energy. In addition, at the time of ligand preparation there was also a number of torsion or ligand torsion which was the number of hinges or rotational positions of the ligand that coul bind to the receptor. The maximum amount of ligand torsion in AutoDock Software was 32, if the ligand torsion exceeded the maximum number of ligands it would be difficult to obtain good anchoring results, because it meant having too many rotational positions that could bind to the receptor. And the ligand torque produced from each compound did not exceed 32 so that the next process could be carried out.

The compounds that had been drawn and converted in 3D were then tethered to the orexin receptor to see the interaction of the compound with the receptor and see which compound had the best interaction. The results obtained showed that all compounds obtained negative Gibbs bond free energy (ΔG). Gibbs energy was a parameter which was produced as a result of molecular docking. This related to the strength and affinity of the interaction between the ligand and the receptor. Where the smaller the bond energy, the stronger the interaction and vice versa. Other parameters that could be used besides bond energy were by looking at the value of KI (inhibition constant) and amino acid residues that interacted with compounds.

Based on the results of the bonding of compounds, it was found that the bonding of cinnamon compounds with orexin receptors had Gibss bond free energy (ΔG) with negative results. So, with these results it could be said that the interaction between the compound and the receptor could take place spontaneously. Then, the next parameter that could be taken into account in predicting the activity of the compound was the value of the inhibition constant (Ki) and the amino acid residue that interacts with the compound.

Based on the results of the tethering, it was shown that the cinnamon compound had interactions with several amino acid residues. However, in the explanation presented by Yin *et al.*[14] that the amino acid residues that interact between suvorexant and orexin receptors through hydrogen bonds are Asn324 and His350 (see Figure 2).

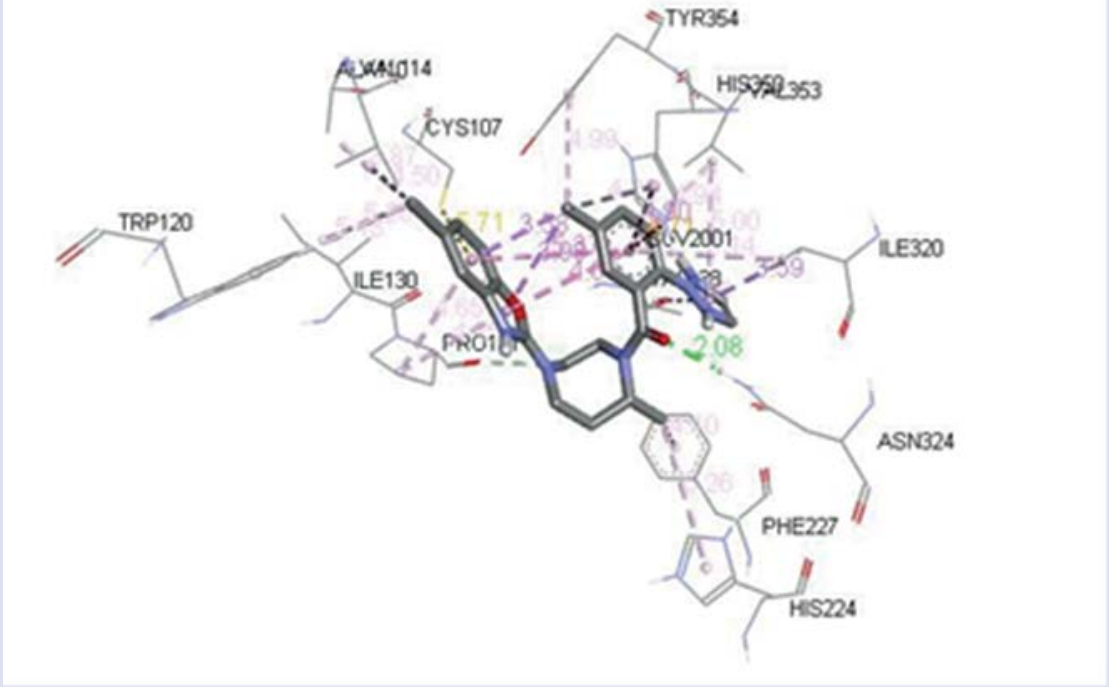

Figure 2: Visualization of the interaction of suvorexant with orexin receptors.

This result was in accordance with the results of the binding of Cinnamic Acid, Coumarin, Quercetin, Methylhidroxy Calcone and Tannin compounds. For Cinnamic Acid compounds had interactions with amino acid residues Asn324 2.04, Coumarin compounds bind to the amino acid residue Asn324 with a bond distance of 2.21, Quercetin compounds bind to Asn324 with a bond distance of 2.84, Methylhydroxy calcone compounds bind to His350 with a bond distance of 1.94 and for Tannin compounds bind to acid residues amino acids with a bond distance of 2.16 while for compounds 1.8 Cineole, Alpha Pinene, Alpha Terpineol, -Caryophyllene, Borneol, Champor, Cinnamyl Alcohol, Cynnamaldehyde, Eugenol, p-Cyemene and Terpinen-4-ol do not bind to amino acid residues such as which had been described by Yin *et al*.[14]

From the results of anchoring compounds, judging from the Gibss bond free energy parameters (ΔG) and the inhibition constant (Ki), the best values were found in Methylhidroxy calcone and Cinnamic acid compounds. The value of Ki would be directly proportional to the value of Gibss (ΔG), which meant that the smaller the value of Gibss (ΔG), the smaller the value of Ki. According to Zheng and Poli[15] the results of Ki if the value was below 100 M, then the compound was a potential enzyme inhibitor. From this statement, there were two compounds that met the criteria for the best Ki value, namely Methylhydroxy calcone and Cinnamic acid compounds. For the Methylhydroxy calcone compound, the Ki value was 5.67 with a Gibss (ΔG) value of -7.16 and for the Cinnamic acid compound, the Ki value was 68.49 and the Gibss (ΔG) value was -5.68 and for the value other compounds. From the results of the tethering of the compounds listed in Table 2.

Actually, research computational methods were being developed to predict the drug-likeness of compounds.[16] Currently it has developed in almost all fields. In search of compounds that are efficacious for drugs from plants. Here are examples, for example, Molecular docking studies and ADME-Tox prediction of phytocompounds from *Merremia peltata* as a potential anti-alopecia treatment,[17] Molecular Modeling of Anti-Alopecia Compounds Found in Sauropus Androgynus,[18] REVIEW: Efficacy, Safety and Drug–Drug Interactions for Insomnia Therapy in COVID-19 Patients[19] and Potential anti-alopecia constituents from *Theobroma cacao*: An *in silico* Study.[20]

When viewed from the Gibss bond free energy parameters (ΔG) and the inhibition constant (Ki), the best values were for Methylhidroxy calcone and Cinnamic compounds. The value of Ki would be directly proportional to the value of Gibss (ΔG), which meant that the smaller the value of Gibss (ΔG), the smaller the value of Ki. According to Zheng and Poli[15] the results of Ki if the value was below 100 M, then the compound was a potential enzyme inhibitor. From this statement, there were two compounds that met the criteria for the best Ki value, namely Methylhydroxy calcone and Cinnamic Acid compounds. For the Methylhydroxy calcone compound, the Ki value is 5.67 with a Gibss (ΔG) value of -7.16 and for the cinnamic acid compound, the Ki value is 68.49 and the Gibss (ΔG) value is -5.68 and for the value. So, when viewed from the Gibss bond free energy parameters (ΔG) and the inhibition constant (Ki) it could be said that Methylhydroxy calcone and Cinnamic acid compounds were compounds that had the best potential to interact with orexin receptors compared to amino acid residues, one of which was hydrogen bond interactions with Asn324 residue on the benzene ring with a bond distance of 1.94. Figure 3 showed interaction of Methylhydroxy calcone with Acid Residues whereas figure 4 showed interaction of Cinnamic acid compounds on orexin receptors with Amino acid residues. Likewise, Cinnamic Acid compounds had amino acid residue interactions, three of which had hydrogen bond interactions on the carbonyl group with Lys327 residues with a bond distance of 1.77 and Arg328 with a bond distance of 1.91 and amino acid residues Asn324 on the benzene ring with a bond distance of 2.04.

ADMET prediction results for methylhidroxy calcone and cinnamic acid

In seeking initial information regarding absorption, distribution, metabolism, excretion and toxicity (ADMET) it is necessary to carry

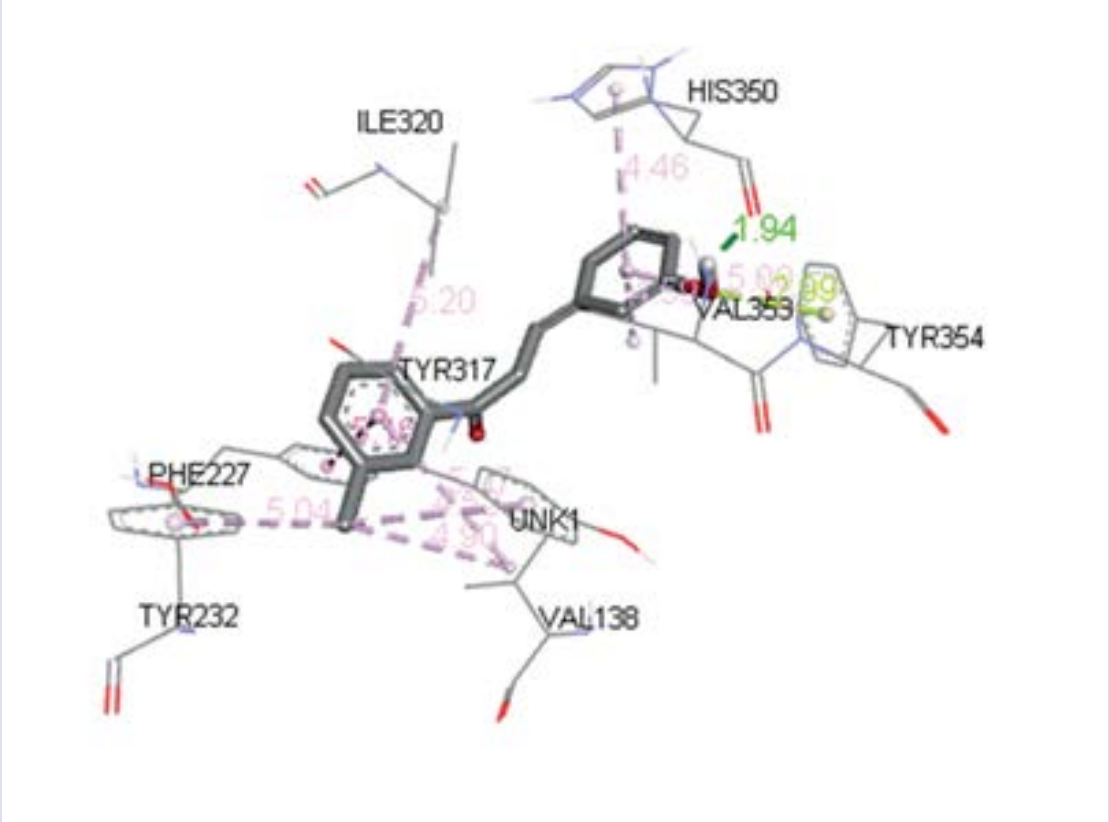

Figure 3: Interaction of methylhydroxy calcone with acid residues.

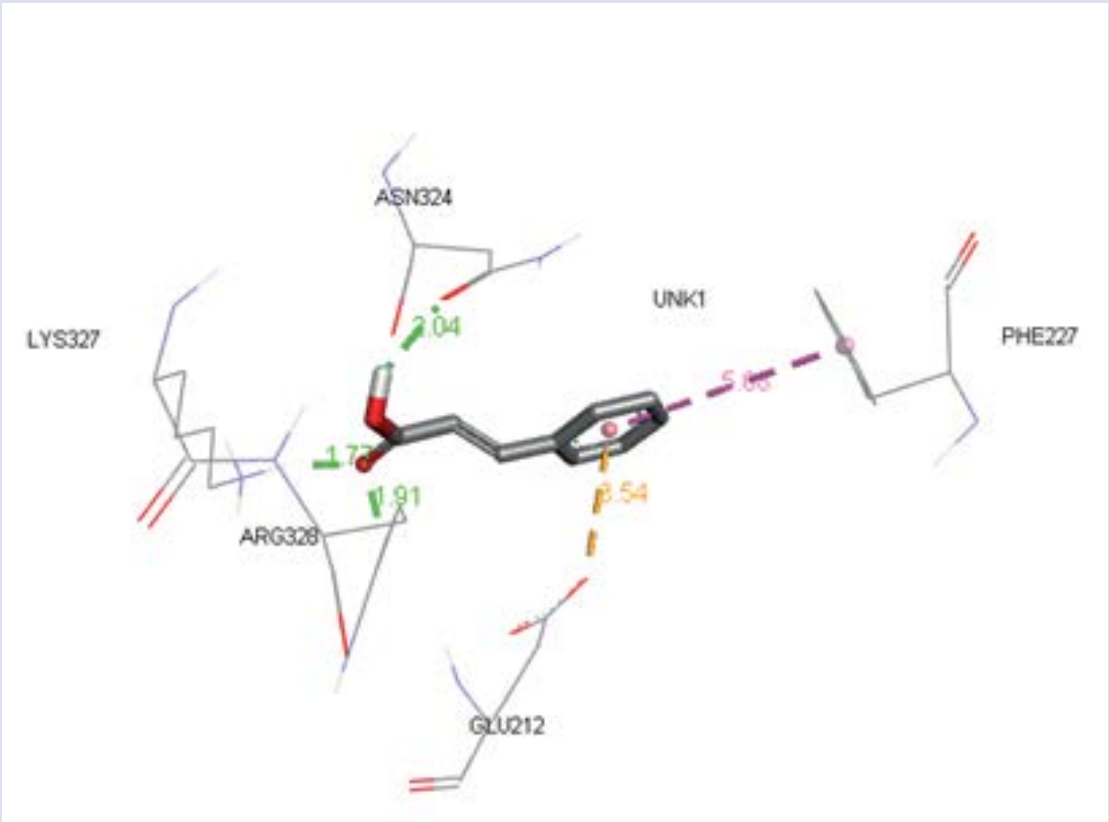

Figure 4: Interaction of cinnamic acid compounds on orexin receptors with amino acid residues.

Table 2: Free bond energy, inhibition constants and amino acid residues.

Compound	ΔG (Kcal/mol)	KI (μM)	Amino acid residues
Cinnamic acid	-5.68	68.49	ASN324
Coumarin	-5.45	100.94	ASN324
Quercetin	-5.06	194.17	ASN324
Methylhydroxy Calcone	-7.16	5.67	HIS350
Tannin	-3.94	1290	ASN324

Table 3: Parameters of ADMET for methylhydroxy calcone and cinnamic acid.

Compounds	Solubility In Water	HIA (Human Intestinal Absorption)	BBB	Hepatoxicity	PPB (Plasma Protein Binding)
Methylhidroxy Calcone	-3.559	0.9907	0.5000	+	0.799
Cinnamic Acid	-2.417	0.9718	0.9344	-	0.757

Notes:
Solubility in water: Slightly soluble in water (-6.0 < x < -2.0)
BBB : High absorption (< 2.0)
: Moderate absorption (2.0~0.1)
: Low absorption (> 0.1)
HIA : poor absorption compounds (0-20%)
: moderately absorbed compounds (20 ~ 70%)
: well absorbed compounds (70 ~100%)
Hepatosis: non-toxic (-)
: toxic (+)
PBB : chemicals strongly bound (< 90%)
: chemicals weakly bounds (> 90%)

out biological screening.[21] The initial stages in the drug discovery process are closely related to the properties of ADMET in a compound and have been carried out for the last decades.[22] Prediction of ADMET properties was carried out *in silico* through the website www.lmmd.ecust.edu.cn with the parameters used including water solubility, BBB (Blood Brain Barrier), hepactocytosis and plasma protein binding. The results of the ADMET parameters can be seen in Table 3.

ADMET prediction was carried out on Methylhidroxy calcone and Cinnamic acid compounds, because from the results of molecular bonding the two compounds obtained the best results compared to other compounds. For water solubility prediction, the two compounds obtained results of -3.559 for Methylhydroxy Calcone and -2.417 for Cinnamic Acid, from these results it indicated that both compounds were soluble in water.

BBB (Blood Brain Barrier) was a microvascular unit that selectively regulates drug permeability to the brain. BBB was done to predict a compound could pass through the blood-brain barrier or it could also be called the ability to penetrate a compound into the blood-brain barrier. This was very necessary because the active compounds in the central nervous system ought cross the brain barrier, while for inactivation the central nervous system ought not cross the barrier because it was related to the prevention of side effects of the central nervous system. Both compounds resulted in poor permeability at the blood brain barrier (low absorption) because the results obtained were less than 0.1, meaning that both compounds had low absorption in the central nervous system. However, the Cinnamic acid compound obtained better results than Methylhidroxy calcone, where the Cinnamic acid compound obtained a result of 0.9344, which meant that the result was close to 0.1 with a moderate absorption rate.

Prediction of HIA (Human Intestinal Absorption) was carried out to see how well these compounds could be absorbed by the intestines. In both compounds, the values (poorly absorption) were obtained because the values obtained were 0.9907 for Methylhydroxy calcone and 0.9718 for Cinnamic acid. This indicated that both compounds had poor absorption in the intestine.

Hepatotoxicity parameter was performed to determine the presence of dose dependent hepatotoxicity in humans. From the results obtained that the compound Methylhidroxy Calcone produces a positive value so that the compound had toxic properties. And for the Cinnamic acid compound it produced a negative value which meant the compound was not toxic.

For prediction Plasma Protein Binding (PPB) was carried out to predict the binding of compounds to carrier proteins in the blood or brain. The results obtained by both compounds showed that the percentage of binding was less than 90% or at the level of chemicals weakly bounds, which means that the predicted two compounds were not strongly bound to plasma proteins.

From the results of the ADMET predictions that had been made, both of them did not get good enough results according to the parameters. However, from the parameter results on the hepactotoxicity of Cinnamic Acid compounds obtained negative or non-toxic results while Methylhydroxy calcone obtained positive results or the compound had toxic properties. Then according to the prediction results of ADMET, the best compound was chosen, which was found in the Cinnamic acid compound so could be used as a new promising anti-insomnia agent.

CONCLUSION

The results of this study indicate that cinnamic acid is a promising new anti-insomnia agent supported by the results of molecular binding which has the lowest Gibss bond free energy (ΔG) and inhibition constant (Ki) compared to other compounds and from ADMET predictions, it shows non-hepatotoxicity.

SIGNIFICANCE STATEMENT

This study discovers Compounds in *Cinnamomum burmannii* namely Cinnamic acid could be used as a new promising anti-insomnia agent.

AUTHOR'S CONTRIBUTION

Resmi Mustarichie: carried out and supervised research, compiled the data and wrote manuscript; Nyi Mekar Saptarini: designed and

supervised the study; Sandra Megantara: co-supervised the research especially docking and admet study. All authors reviewed the manuscript. Not to mentioned that these authors have experiences in *in-silico* and ADMET researches.

CONFLICTS OF INTEREST

Authors declared that they have no conflicts of interest.

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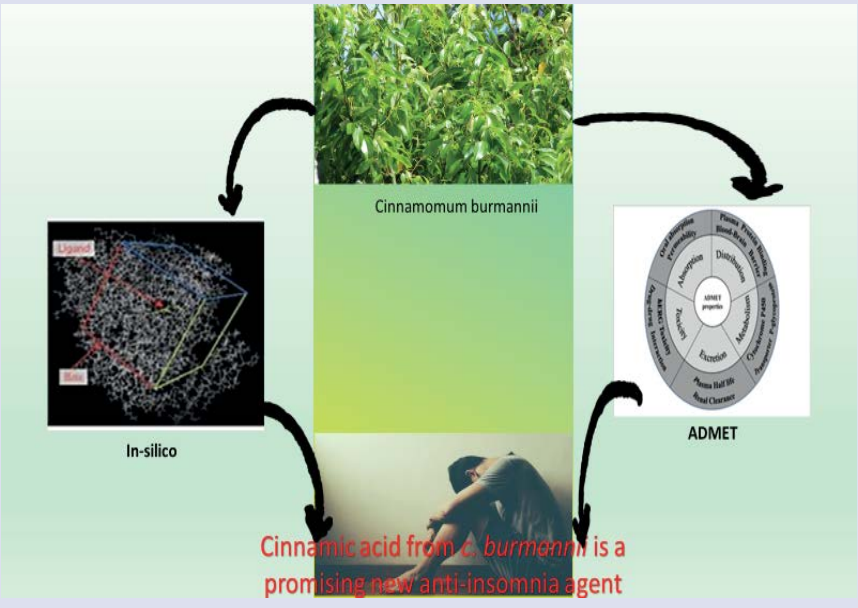
GRAPHICAL ABSTRACT



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