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Original Article

MOLECULAR DOCKING OF *CYMBOPOGON NARDUS* (L.) RENDLE COMPOUNDS AS A PROTEASE INHIBITOR OF SARS-COV-2

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ABSTRACT

Objective: The study aimed to obtain active compounds from *Cymbopogon nardus* as candidates for protease inhibitor of SARS-CoV-2 virus by assessing the ligand-binding affinity in the binding pocket of SARS-CoV-2 main protease protein.

Methods: Molecular docking as a protease inhibitor of SARS-CoV-2 was carried using computational software Molegro Virtual Docker (MVD); computational docking was carried using receptors with Protein Data Bank (PDB) were also used to compare the affinity strength of the test compounds against the protease receptor (code of 5R81). The compounds of Cymbopogon nardus were optimized before docking using ChemDraw and minimized energy using Chem3D. Visualization of the docking result by using Discovery Studio and pkCSM was utilized to perform a pharmacokinetic and toxicological analysis (ADMET).

Results: The result showed geranyl acetate, elemol, citronellal, and citronellyl acetate compounds from *Cymbopogon nardus* has a rerank score more negative than native ligand from 5R81 receptor as a protease inhibitor of SARS-CoV-2.

Conclusion: *Cymbopogon nardus* can be developed as an antivirus with the mechanism of a protease inhibitor of SARS-CoV-2 candidates after further experimental tests.

Keywords: SARS-CoV-2, Main protease, *Cymbopogon nardus*, Molecular docking

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INTRODUCTION

Coronavirus disease (COVID-19) is a respiratory infectious disease caused via a novel virus strain, SARS-CoV-2 [1]. This virus is a new type of virus from the family of coronaviruses that reason diseases of the respiratory system. COVID-19 is transmitted through direct contact with patients, droplets when coughing/sneezing, as properly as hands contaminated with the virus when touching the nose and eyes [2]. In the past two decades, two different coronaviruses have caused global outbreaks, specifically SARS-CoV (2002–2003) and Middle East respiratory syndrome coronavirus [3].

SARS-CoV-2 is a single-stranded RNA (ribonucleic acid) enveloped virus, targeting cells via the structural protein Spike (S protein) that binds with the angiotensin-converting enzyme 2 (ACE2) receptor [4]. After receptor binding, viral particles use the host cell's receptors and endosomes to enter the cell. Transmembrane serine protease 2 (TMPRSS2) protein helps cell entry via S protein [5]. Once inside the cell, viral polyproteins encoding the replication transcriptase complex are synthesized. In this, the virus synthesized RNA through RNA polymerase which is dependent on the RNA. Structural proteins are synthesized towards the completion of assembly and launch of viral particles [5]. The steps of this viral life cycle supply a possible target for drug therapy. The targets of these drug products consist of ACE2, S protein, and TMPRSS2 (type 2 transmembrane serine protease) as properly as 3-chymotrypsin like protease (3CL) a protease inhibitor [6].

Docking ligand-protein is a drug development process used to virtually predict ligand-protein complex. The docking result is a rerank score that is proportional to the total energy of the ligand-protein bond. The rerank score of a compound in contrast to the rerank score of any other compound may also explain why one compound is more effective than another. The smaller the rerank score docking results, means the ligand-protein complex is getting more steady and potent [7].

Cymbopogon nardus contains compounds such as citronellal, citronellol, nerol, geranyl acetate, elemol, and gemacren-4-ol. The essential oils of *Cymbopogon nardus* were assessed for acaricidal activity against Rhipicephalus microplus [8]. The study aims to obtain active compounds from *Cymbopogon nardus* as candidates for protease inhibitor of SARS-CoV-2 virus by molecular docking method to find new drug candidates are obtained as antivirals.

MATERIALS AND METHODS

Material

The materials used are the crystal structure of COVID-19 main protease (PDB: 5R81). Chemical compounds of *Cymbopogon nardus*. Software used in the form of PDB, PubChem, pkCSM, Molegro Virtual Docker, ChemDraw, and Discovery Studio running on Hp 14s-dk1122AU AMD Athlon Gold 3150U laptop hardware; 4 GB RAM; SSD; VGA: AMD Radeon Graphics.

Preparation of compound test and comparison

Test compounds are drawn using ChemDraw software and minimization energy using Chem3D software.

Validation of the docking protocol

Internal validation is done by redocking the native ligand of the receptors inside the cavity using Molegro Virtual Docker software and obtaining rerank score and RMSD value.

Docking of compound tests

Test compounds in docking against receptors using Molegro Virtual Docker software is obtained rerank score. The rerank score results are compared with native ligand and determined by the compound with the best rerank score for visualization and toxicological analysis.

Result of visualization

Visualizes the docking result by using Discovery Studio software to find out the interactions between ligand-protein complexes.

Prediction of toxicity of the active compound *Cymbopogon nardus*

Prediction of toxicity of active compounds is done by inserting the smile name of the test compound into the pkCSM program, which further obtained complete data about the toxicity properties of each of these compounds [9].

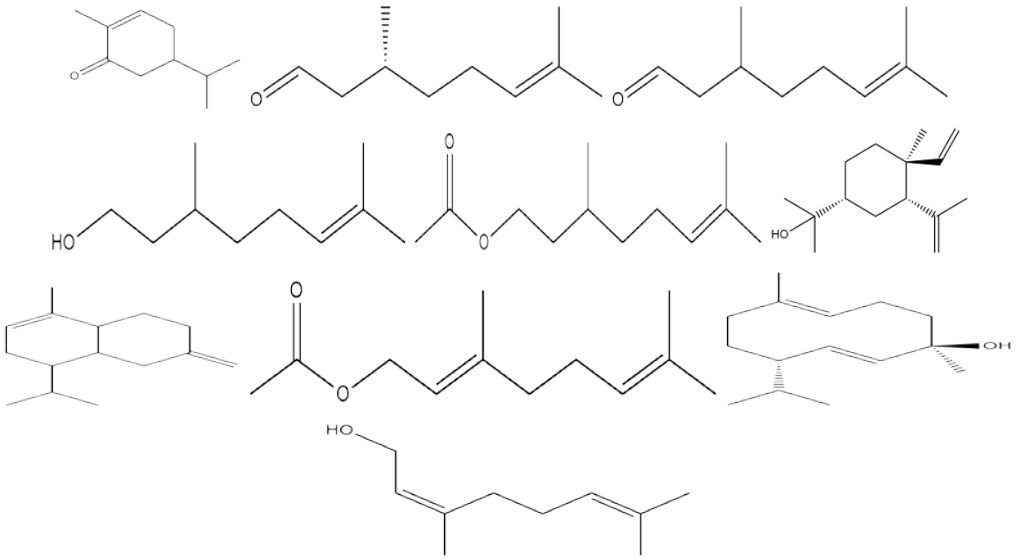

Fig. 1: Structure of *Cymbopogon nardus*

RESULTS AND DISCUSSION

Analysis of receptor used

The crystal structure of COVID-19 main protease (PDB: 5R81) is downloaded through the Protein Data Bank website. 5R81 is the crystal structure of COVID-19 main protease in complex with Z1367324110 with native ligand in the front of 1-methyl-3,4-dihydro-2~{H}-quinoline-7-sulfonamide (RZJ). The selection of receptors is used based on internal validation in the form of RMSD values by redocking native ligands using Molegro Virtual Docker software. RMSD values from 5R81 amounted to 1.17269 Å. The smaller the value of the RMSD means, the more similar the position of the ligand docking results with its native ligand [10].

Analysis of docking results

There were 10 compounds from *Cymbopogon nardus* that were tested for affinity as protease inhibitors of SAR-CoV-2 against receptors 5R81. All compounds are tested *in silico* using the molecular docking method. Docking is performed on the active side of binding receptors 5R81 then rerank score is calculated on each pose formed. Rerank score indicates Gibbs' free energy. Gibbs energy is energy that if the value is getting negative means that the bond energy between ligand and protein is getting bigger in value. The rerank score of the docking tests compound is compared to the rerank score of the native ligand in the receptor.

In able 1 described the docking results on the 5R81 receptor, there are 4 compounds of *Cymbopogon nardus,* namely geranyl acetate, elemol, citronellal, and citronellyl acetate, are predicted to have a better affinity in inhibiting the main protease of SARS-CoV-2 receptor than the native ligand in the receptor as evidenced by more negative rerank scores. Geranyl acetate has the lowest rerank score.

Visualization of ligand-protein interaction

Visualization of molecular docking results provides information about the interaction between proteins and ligands. Visualization is done using Discovery Studio software (fig. 2-5). It can visualize amino acids that bind to active compounds and determine the distance of hydrogen bonds in angstrom units (Å) between candidate drug compounds and amino acids present among the main protease of the SARS-CoV-2 receptor.

Prediction of toxicity of the active compound *Cymbopogon nardus*

Analysis of toxicity predictions with the pkCSM method. In this study, the results of predictions of toxicity of test compounds with pkCSM (table 2), explained that all test compounds are not hepatotoxic and are not carcinogenic, but all Test compounds are irritative of the skin. Based on this, it can be said that all test compounds that are active compounds of *Cymbopogon nardus* are predicted to be safe, not toxic.

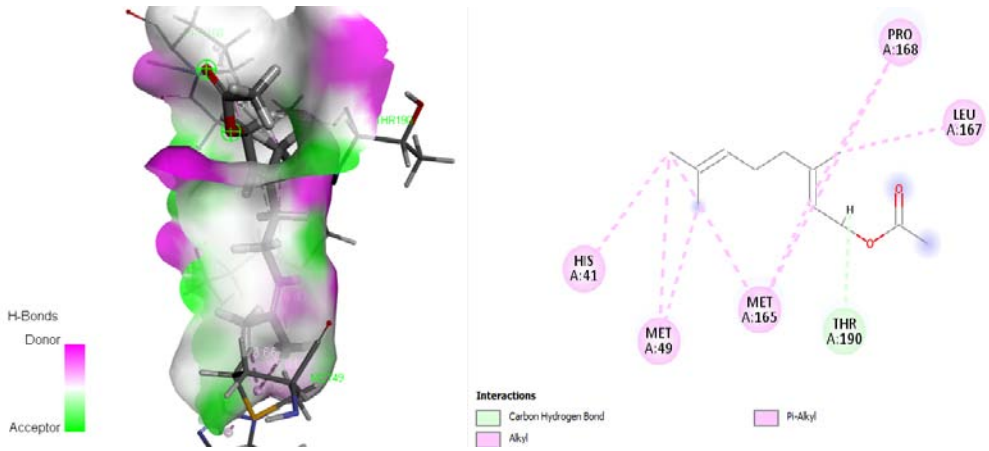

Fig. 2: Complex geranyl acetate in 5r81 receptor

Table 1: Docking results in 5r81 receptor

Ligand	Moldock score	Rerank score	HBond
Geranyl acetate	-96.909	-79.4314	0
Elemol	-98.0136	-76.084	-6.63918
Citronellal	-89.6115	-74.1933	-1.73086
Citronellyl acetate	-87.1007	-73.0066	-1.13751
RZJ_1001 [A]	-86.0678	-72.6502	-2.48653
(R)-Citronellal	-87.2109	-72.5356	-0.825931
Citronellol	-87.0233	-70.8868	-3.74775
Nerol	-85.5706	-70.2794	-2.22226
Germacren-4-ol	-79.3095	-65.9616	-2.5
gamma1-Cadinene	-79.8168	-63.2856	0
(-)-Carvotanacetone	-70.5572	-60.5992	-0.443672

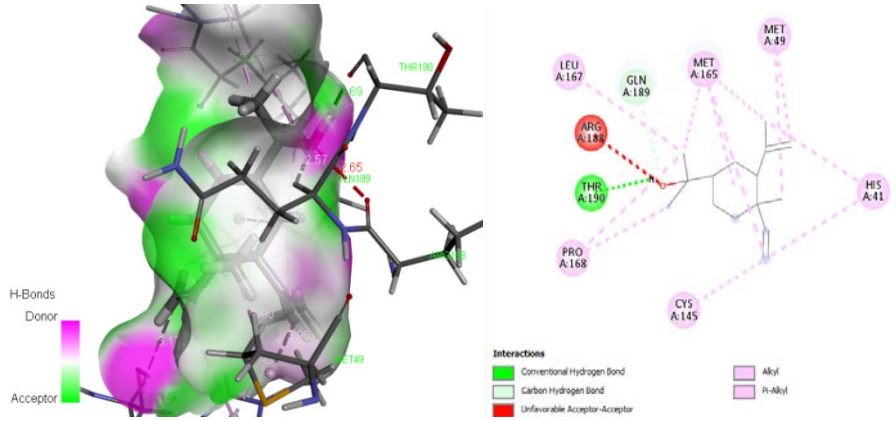

Fig. 3: Complex elemol in 5R81 receptor

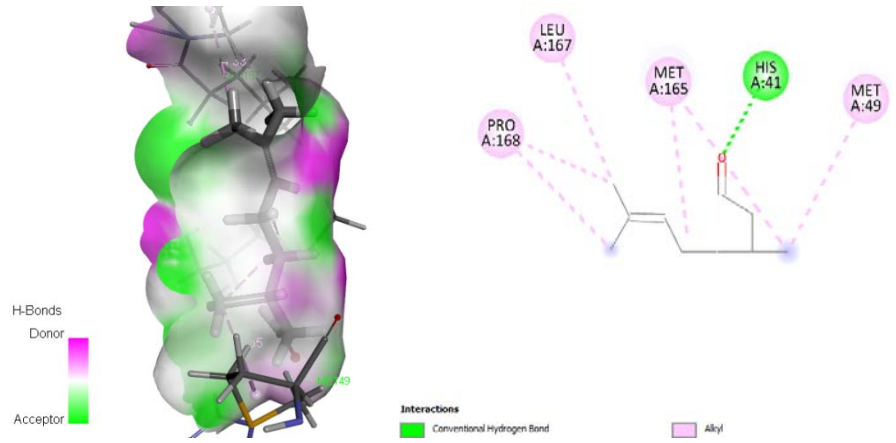

Fig. 4: Complex citronellal in 5R81 receptor

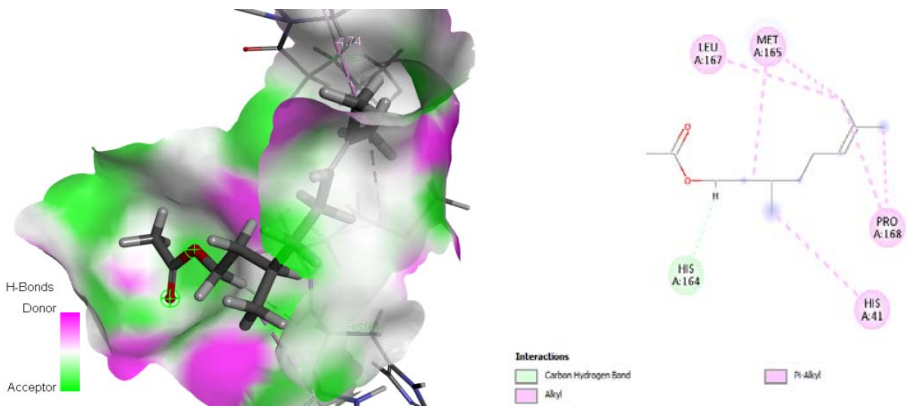

Fig. 5: Complex citronellyl acetate in 5R81 receptor

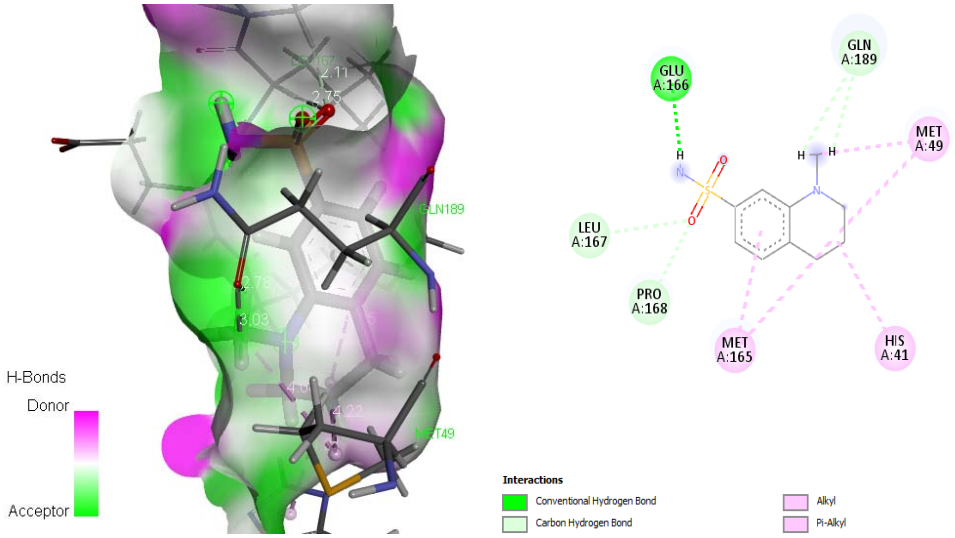

Fig. 5: Complex native ligand (RZJ) in 5R81 receptor

Table 2: Prediction of toxicity with pkCSM

Compounds	Ames toxicity	Hepatotoxicity	Skin sensitization	Oral rat acute toxicity (LD50) (mol/Kg)
Geranyl acetate	No	No	Yes	1.683
Elemol	No	No	Yes	1.686
Citronellal	No	No	Yes	1.634
Citronellyl acetate	No	No	Yes	1.717

CONCLUSION

Cymbopogon nardus can be developed as an antivirus with the mechanism of a protease inhibitor of SARS-CoV-2 candidates after further experimental tests.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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