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RESEARCH ARTICLE

In silico approach of antiviral compound from *Cymbopongon citratus* as the main protease SARS-CoV-2 inhibitor

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Abstract

A pandemic known as COVID-19 is brought on by the RNA virus SARS-CoV-2. SARS-CoV-2 has some protease enzymes, such as main proteases (Mpro), that regulate the expression of viral non-structural proteins. The Mpro protein is a possible target for SARS-CoV-2 antiviral therapy because the inhibition of Mpro will disrupt the virus replication process and stop the virus life cycle. Lemongrass is an Indonesian spice with bioactive compounds whose benefits have not been widely explored, especially as an antiviral for SARS-CoV-2. This study aimed to identify potential bioactive chemicals in lemongrass that have antiviral properties for treating COVID-19. This methodology research began by preparing the bioactive compounds of lemongrass and Mpro protein. Using Lipinski's rule of five, the nine bioactive chemicals found in lemongrass were examined to see how similar they were as therapeutic compounds. Next, PyRx 0.8 (Virtual Screening Tool) and PyMOL were used to perform molecular docking and its interaction with the Mpro protein. Diethyl phthalate has antiviral and anti-inflammatory activity with low binding energy (-5.8 kcal/mol) for Mpro and is stably bound (RMSF < 3Å) via hydrophobic bonds (His41, Met165) and hydrogen bonds (Phe140, His163, His164, Glu166, Gln189). It is concluded that diethyl phthalate on lemongrass demonstrated high promise as an inhibitor of SARS-CoV-2 viral replication based on the findings of the comprehensive investigation of these bioactive chemicals.

1. INTRODUCTION

The coronavirus illness, or COVID-19, has spread quickly to more than 200 nations worldwide since 2019. The virus that causes COVID-19, which has mutated into other subtypes and resulted in almost 67 million illnesses and 1.5 million deaths, is the SARS-CoV-2 virus (1). As a result, the COVID-19 epidemic is now considered a pandemic and a serious threat to global health (2).

The papain-like protease (Plpro) and main-protease (Mpro) encoded by the SARS-CoV-2 virus's genetic material control the production of the virus' nonstructural proteins. PLpro was involved in the replicase-transcriptase complex integration, host reaction destruction, and viral protein maturation and cleavage. Mpro, a different protease, is employed to cause the maturation and cleavage of viral proteins over viral replication (3-4). Because Mpro was discovered and made public in February 2020, out of the two varieties of viral protease, it is the protein with the most easily accessible crystal structure (5). Previous research explains that several drugs containing a combination of antivirals (for example, telbivudine and ribavirin) and vitamins have been chosen for SARS-CoV-2. Kandeel and Al-Nazawi's (5) research regarding the role of the Mpro protein proves that several types of compounds can act as Mpro inhibitors and have potential as a treatment for COVID-19.

The Mpro of SARS-CoV-2 plays a critical role in the virus's replication cycle, making it an essential target for antiviral therapy. Mpro cleaves the viral polyprotein into functional proteins necessary for assembling new virions, a process fundamental for the virus to propagate within the host. Inhibiting Mpro disrupts viral replication, thereby reducing the viral load and potentially alleviating the severity of infection. Due to its central function in the life cycle of SARS-CoV-2,

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Mpro is considered a prime therapeutic target. As a result, Mpro inhibitors have become crucial in reducing the virulence and spread of SARS-CoV-2 by preventing the virus from producing the proteins required for successful replication (6).

The high replication rate of SARS-CoV-2 has led to a rapid increase in the number of cases and deaths caused by COVID-19. Due to the important role of the Mpro enzyme in SARS-CoV-2 replication, the search for bioactive compounds that can inhibit Mpro is an opportunity for antiviral therapy for SARS-CoV-2. Studies on the structure of SARS-CoV-2 Mpro and the impact of its inhibition on the disrupting of the expression of SARS-CoV-2 non-structural proteins have been studied. The study emphasized the potential of Mpro inhibitors as a promising avenue for developing antiviral treatments for COVID-19 (6). Several small molecules have been designed and tested to bind specifically and inhibit the Mpro of SARS-CoV-2. As a result, the inhibition of Mpro significantly reduces viral replication in vitro. This research contributed to the identification of lead compounds for further development into clinical inhibitors against COVID-19 (7). In addition, Jin et al. (8) focused on synthesizing novel Mpro inhibitors by analyzing the enzyme's crystal structure and assessing the binding of potential inhibitors. The researchers found that specific inhibitors, such as N3 and other peptidomimetic compounds, effectively inhibited the activity of Mpro, which consequently hindered SARS-CoV-2 replication in laboratory models. This work laid the foundation for the development of Mpro-targeted therapies.

As a country with the second highest biodiversity wealth in the world, Indonesia has a lot of medicinal potential from natural ingredients, such as herbal plants. The use of herbs is a cultural heritage of the Indonesian people, especially those from Jawa (9). Consuming herbal plants is believed to increase stamina and endurance to prevent several diseases (10). Lemongrass (*Cymbopogon citratus*), an Indonesian spice, contains various bioactive compounds such as organic acids, fiber, phenolics, alkaloids, flavonoids, terpenes, and lipids. Some of these, especially citral, luteolin, and quercetin, have shown antiviral activity in in vitro studies by disrupting viral envelopes or inhibiting viral replication. However, their effectiveness in in vivo settings still needs further investigation.

Although many Mpro inhibitors have been discovered, these compounds are synthetic chemical compounds that can cause virus resistance effects (11). Therefore, the exploration of new compounds is still needed. Natural ingredients have holistic effects, and many compounds are efficacious as Mpro inhibitors. Previous studies have shown that the bioactive components of *C. citratus* have significant antimicrobial, anti-inflammatory, antioxidant, and antidiabetic activities. Furthermore, research by Odukoya et al (12) showed that essential oils from *C. citratus* exhibit strong anticancer and antimicrobial properties, supporting their use in traditional medicine. Unlike previous studies, this study attempts to determine the potential and effectiveness of lemongrass bioactive compounds as SARS-CoV-2 antiviral agents using artificial intelligence (AI)-based in silico methods.

Lemongrass contains bioactive compounds, such as citral (comprising geranial and neral), flavonoids, and phenolic acids, which have been shown to possess potential antiviral properties. These compounds are fascinating for studying Mpro inhibition, a crucial enzyme in replicating viruses such as SARS-CoV-2. Some bioactive compounds, in particular, have been identified as potential inhibitors of Mpro by binding to its active site. This inhibition mechanism blocks the enzyme's ability to process viral polyprotein and inhibit viral replication. In addition, other compounds present in lemongrass may act synergistically to enhance this inhibitory effect, making it a promising natural source for developing antiviral therapies targeting Mpro (12).

This in silico study used the bioactive chemical ligand of lemongrass from PubChem and the Mpro SARS-CoV-2 structure from the Protein Data Bank (PDB). In addition, molecular simulation methods were employed to characterize the antiviral candidate Mpro protein-ligand bond. With all of that, this study could contribute to the development of low-cost, plant-based antiviral therapies. Also, it will raise awareness among the general population about the health advantages of Indonesian plants, particularly lemongrass.

2. MATERIALS AND METHODS

2.1. Preparing the sample

The SARS-CoV-2 Mpro protein's three-dimensional (3D) structure was extracted in .pdb format from PDB using ID: 6WTT. This protein structure was selected based on its good resolution (2.15 Å) and lack of mutations. In addition, the 6WTT Mpro protein model featured 7,430 non-hydrogen atoms, which is the most of any model. Using the PyMOL software, the original ligand and water content were eliminated to sterilize the 3D structure of the Mpro protein.

All the *Cymbopongon citratus* antiviral candidate compound contents were retrieved from research conducted by Hartatie *et al*. (13). All bioactive chemicals' 3D molecular structures in canonical SMILES and .sdf formats were acquired from PubChem. Next, PyRx 0.8 software was used to perform a minimization process on the ligand's complete molecular structure.

2.2. Drug-Likeness Molecule Analysis

Drug similarity analysis was performed on the 3D structure of the ligand for the bioactive chemical *C. citratus*, which was acquired from PubCHem, using the Lipinski's Rule of Five web server (www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp). Five requirements must be met for a drug molecule to be considered

similar according to Lipinski's Rule of Five: molecular mass > 500 Dalton, high lipophilicity (LogP) > 5, hydrogen bond donor (HBD) > 5, hydrogen bond acceptor (HBA) > 10, and molar refraction (MR) 40-130 (14).

2.3. Prediction of the Lemongrass Phytosterol Compounds' Biological Activity

Compounds from *C. citratus* were tested for bioactivity using the PASS online server (http://way2drug.com/PassOnline/). The antiviral and anti-inflammatory activities were chosen for forecasting. Since that result indicated computational evidence, the potential activity (Pa) score below 0.3 (medium confidence) was chosen as the benchmark. Additionally, in order to prohibit the compound's action in the human body, the Pa score needs to be greater than the probability score (Pi) (15).

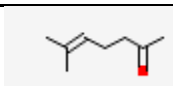
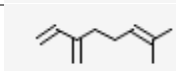
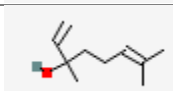
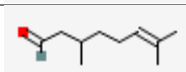
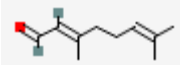
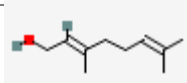
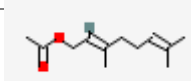
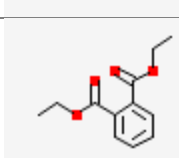
2.4. Virtual Screening and Molecular Visualization

The AutoDock Vina 1.1.2 program on PyRx was used to analyze the docking simulations of the binding of *C. citratus* ligand compounds to the Mpro protein domain. The Mpro docking grid coordinates are directed at position (Å) X:18.4512 Y:28.7984 Z:13.0910 and dimensions (Å) X:69.7957 Y:97.4120 Z:102.1739. This is performed to determine the optimal binding of *C. citratus* ligand compounds to the Mpro protein, considering the binding affinity of the ligand to the protein (16,17). The binding of the *C. citratus* compound ligand to the Mpro protein was then visualized in three dimensions using PyMOL software, and staining selection was performed to distinguish the target protein's chains and the type of bound ligand.

2.5. Molecular Dynamics Simulation

The flexibility and stability of the binding between ligands and proteins can be visualized through molecular dynamics simulations to resemble real biological process conditions. Online molecular dynamics simulations were performed using CABS-flex 2.0 (http://212.876.3.12/CABSflex2/index). The purpose of CABS-flex is to compute the root mean square fluctuations (RMSF), a measure of the flexibility of proteins. This software is used to track the amplitude of atomic mobility during molecular dynamics simulations. The molecular dynamics are considered stable if the RMSF value of ligand-protein binding is within 1-3 Å (18).

Table 1. Sample preparation results of the *Cymbopongon citratus* ligand compound

Bioactive Compound	CID	Formula	Cannonical SMILES	2D Structure
6-Methyl-5-hepten-2-one	9862	$C_8H_{14}O$	CC(=CCCC(=O)C)C	
Beta-Myrcene	31253	$C_{10}H_{16}$	CC(=CCCC(=C)C=C)C	
Linalool	6549	$C_{10}H_{18}0$	CC(=CCCC(C)(C=C)O)C	
Citronella	7794	$C_{10}H_{18}0$	CC(CCC=C(C)C)CC=O	
Citral	638011	$C_{10}H_{16}O$	CC(=CCC/C(=C/C=O)/C)C	
Trans-geraniol	637566	$C_{10}H_{18}O$	CC(=CCC/C(=C/CO)/C)C	
Geranyl acetate	1549026	$C_{12}H_{20}O_2$	CC(=CCC/C(=C/COC(=O)C/C)C	
Patchouli alcohol	10955174	$C_{15}H_{26}O$	C[C@H]1CC[C@@]2([C@@]3([C@H]1C[C@H](C2(C)C)CC3)C)O	
Diethyl phthalate	6781	$C_{12}H_{14}O_4$	CCOC(=O)C1=CC=CC=C1C(=O)OCC	

3. RESULTS AND DISCUSSION

3.1. Lipinski's Rule of Five Analysis

Using Lipinski's rule of five, nine bioactive compounds of *C. citratus* were predicted as druglike molecules (19). Determination of druglike molecules based on the following criteria: molecular mass must be less than 500 Da, lipophilicity (LogP) less than 5, hydrogen bond donor (HBD) less than 5, hydrogen bond acceptor less than 5, and molar refraction between 40 and 130. Table 2 shows the results of drug-likeness analysis of nine *C. citratus* compounds using Lipinski's rule of five. According to this study, all the nine chemical components found in lemongrass have been analyzed and proven as druglike molecules and can be used for medications (20).

Fulfilling the five requirements of the Lipinski drug similarity test indicates that the molecule has great potential to become a drug. A good drug molecule has a molecular weight of less than 500 Daltons. Molecules with a smaller molecular weight tend to be more stable and more easily penetrate cell membranes. This indicates good drug bioavailability. Molecules that are too large may have difficulty being absorbed through the digestive tract or entering target cells. In addition, larger molecules can exhibit more complex and less efficient metabolism. Molecules weighing <500 Da tend to be more stable and can pass through various biological barriers better (13).

A good drug molecule is a molecule that has small HBD and HBA values. High HBD and HBA values make the molecule have poor solubility in lipid membranes, so that it can inhibit the efficient absorption of the molecule. Hydrogen bonds with too many molecules result in the molecule not being lipophilic enough to pass through the cell membrane. In addition, molecules with HBD and HBA that are too high may be more easily degraded or have inefficient metabolism (13).

A LogP value that is too high indicates that the molecule is very lipophilic, which can make it difficult for the molecule to dissolve in water, reducing its solubility and bioavailability. Conversely, a very low LogP indicates a very hydrophilic molecule, which may not be able to penetrate the cell membranes well. Therefore, a LogP value between 1 and 5 indicates a good balance between water solubility and lipid solubility, which is optimal for oral drug absorption (13).

Molar Refractivity (MR) is a measure that indicates the size and shape of a molecule and how easily it can interact with its biological environment. An MR value between 40 and 130 indicates that the molecule is neither too big nor too small, has an ideal size distribution for cell penetration, and is likely to have good biological activity. Molecules with too high an MR may be very large or have very complex structures, which reduces their ability to distribute to the right place in the body or interact with their targets effectively (13).

3.2. PASS Analysis

The PASS online server analyzes the bioactivity potential of nine natural compounds of *C. citratus*. The Pa and Pi scores for each compound provide information on the predicted bioactivity of the compounds contained in lemongrass. According to the research objectives, a Pa score of greater than 0.3 indicates the ability to have activity (Figure 1). This study only assessed two components of bioactivity, 3C-like protease (Human Coronavirus) inhibitor and anti-inflammatory, because we do not want the compounds in lemongrass that have the potential to be SARS-CoV-2 antivirals to cause an inflammatory response in the patient's body. According to the findings, two compounds had protease coronavirus inhibitor potential, and five compounds had anti-inflammatory potential (Pa >0.3). Based on these findings, two compounds have coronavirus protease inhibitor and anti-inflammatory potential, namely diethyl phthalate and patchouli alcohol. However, of the two compounds, DEP has 3C-like protease (human coronavirus) inhibitor (Pa > 0.3) and anti-inflammatory (Pa > 0.4) activities. This makes diethyl phthalate (DEP) a prime candidate for the SARS-CoV-2 antiviral that does not cause inflammatory reactions.

Table 2. Results of drug molecule similarities Lipinski *Cymbopongon citratus*

Bioactive Compound	Molecular Mass (< 500 Da)	HBD (< 10)	HBA (< 5)	LogP (< 5)	MR (40 – 130)
6-Methyl-5-hepten-2-one	126	0	1	2.322	39.346
Beta-Myrcene	136	0	0	3.475	48.002
Linalool	154	1	1	2.670	49.486
Citronella	154	0	1	2.958	48.510
Citral	152	0	1	2.878	48.486
Trans-geraniol	154	1	1	2.671	49.508
Geranyl acetate	196	0	2	3.242	59.055
Patchouli alcohol	222	1	1	3.610	66.067
Diethyl phthalate	222	0	4	2.040	58.355

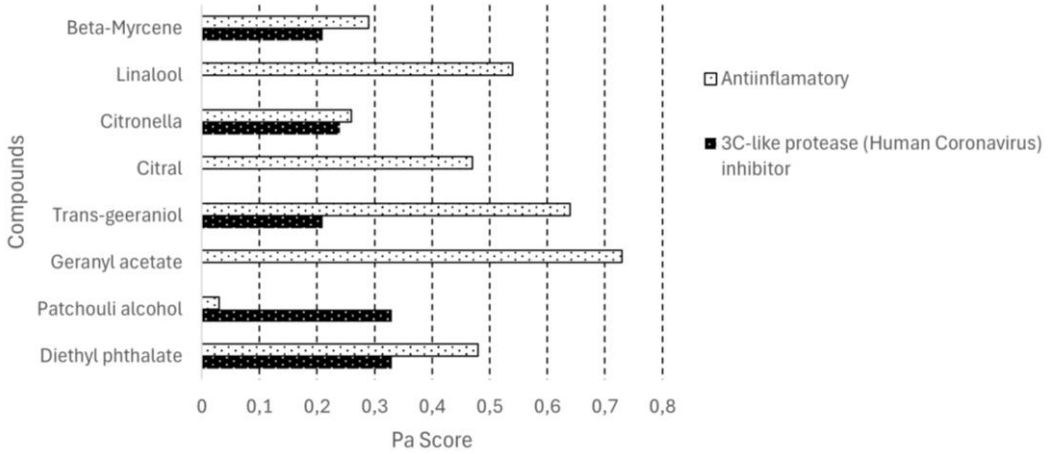


Figure 1. Antiviral and anti-inflammatory properties of the *C. citratus* compounds.

3.3. Molecular Docking Results

The docking simulations between the DEP and Mpro proteins were performed using the PyRx software. The Vina Search Space has been maximized with grid docking center (Å) X:18.4512 Y:28.7984 Z:13.0910 and dimensions (Å) X:69.7957 Y:97.4120 Z:102.1739. The results of DEP docking showed low binding energy (-5.8 kcal/mol) to the Mpro protein. A lower (more negative) binding energy generally indicates a stronger interaction. This stronger binding can inhibit substrate binding in the enzymes. In addition, a ligand with a lower binding energy could be a more potent inhibitor because it is more likely to occupy the active site effectively. In this case, DEP interacts with the Mpro binding site, possibly through multiple non-covalent interactions such as hydrogen bonds, van der Waals forces, or hydrophobic interactions. This efficient binding allows DEP to bind tightly to the active site of SARS-CoV-2 Mpro as an inhibitor (21).

Mpro, a protein of the SARS-CoV-2 virus, was chosen as the target protein in this study because it is crucial for controlling viral protein synthesis and genetic material replication (22). PyMOL software was used in this study's docking visualization to color and choose different structures (Figure 1). An electron cloud that is transparent and features a blue cartoon structure was used to visualize the Mpro target protein. Using the PoseView program in the ProteinPlus online portal, the chemical binding with the lowest bond energy was examined to determine the position and type of bond on the molecular contacts in two dimensions (23).

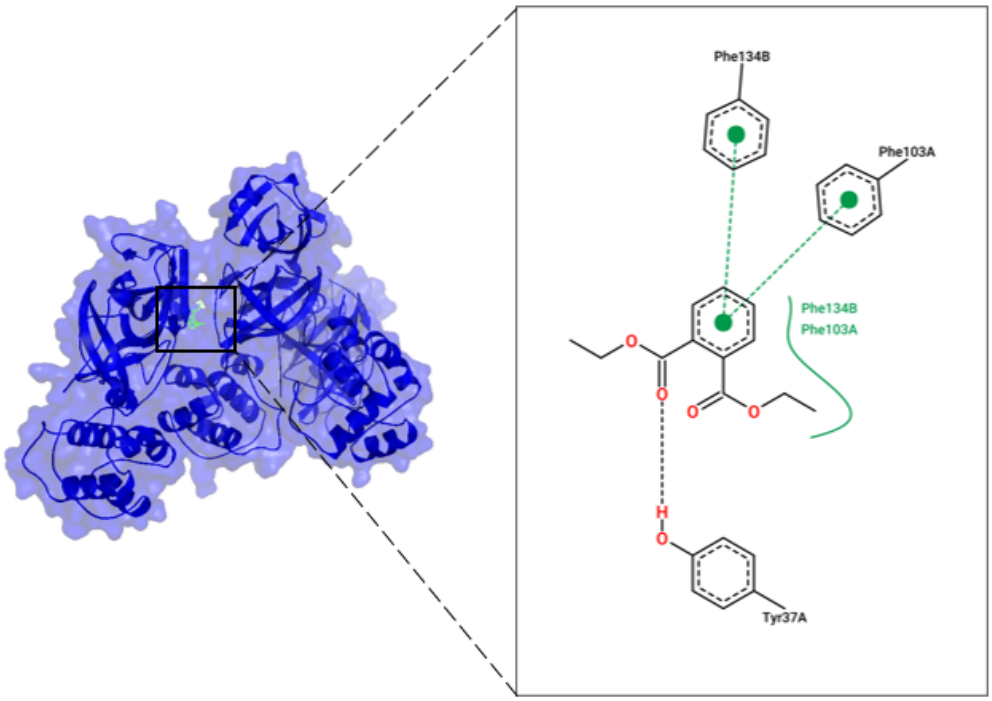


Figure 2. Visualization of the chemical interactions between Mpro proteins and DEP compounds. The green line and dot represent a hydrophobic bond, and the black dotted line represents a hydrogen bond.

The protein-ligand connection is directly depicted in Figure 1 by a dotted line. The hydrophobic interaction of the ligand-protein is represented by the splign portion. The hydrophobic interactions at Phe103 and Phe134 and the hydrogen bonds at Tyr37 bind the compound DEP to the Mpro domain of SARS-CoV-2 (Figure 2). Several parameters, including molecular weight, hydrogen bonds, size, hydrophobic interactions, and shape, are considered when describing the formation of molecular bonds (24).

The simulation's residue-by-residue variations are displayed on the fluctuation plot. The plot's y-axis displays the amino acid residue index, while the x-axis displays the RMSF value (Å) (25). DEP has the lowest free energy, according to a molecular docking analysis performed with Mpro, and the protein fluctuation is still below the 3 Å RMSF criteria (18). As a result, the DEP's structure is considered stable. The Mpro-DEP complex also found residues 191 and 49-51. Variations in RMSF suggest that variations in ligand conformation will ultimately impact the flexibility of proteins (26). The RMSF values of Mpro-DEP complex molecular dynamics were 0.3150 (Phe103) and 2.4050 (Phe134) for the hydrophobic interaction and 0.0970 Å for hydrogen bond (Tyr37).

Protein-ligan connections are necessary for every process in all living organisms. Ligands can facilitate biological identification at the subatomic level and cell signal transmission. Since DEP binds to SARS-CoV-2 Mpro with the lowest binding energy and interacts with the virus through hydrophobic and hydrogen interactions, it may be a viable option for creating and developing COVID-19 therapy medications (27). DEP has an atomic mass of 222 Da, a molar refraction of 58.355, no hydrogen bond donor, four hydrogens bonds acceptors, and a LogP of 2.040, which all satisfy Lipinski's rule of five and qualify it as a drug-like molecule (Table 2). Molecular dynamics simulations demonstrated that diethyl phthalate effectively interacts with SARS-CoV-2 Mpro, suggesting that it may be used therapeutically to cure SARS-CoV-2 infection by suppressing Mpro, which will ultimately cause its failure virion formation. An extensive virtual screening process revealed that the best leads were the chemicals derived from lemongrass. In this instance, there has been discussion on the potential utility of *C. citratus*, a bioactive molecule, as an Mpro SARS-CoV-2 inhibitor. It is highly suggested to conduct both in vitro and in vivo studies to evaluate the therapeutic efficacy of experimentally created ligands before progressing with clinical trials (28).

Lemongrass (*Cymbopogon citratus*) is a widely available plant, and its essential oils contain various bioactive compounds, including DEP. The use of natural plant-derived substances for antiviral applications is gaining attention due to their potential to offer eco-friendly alternatives to synthetic chemical agents. Leveraging such compounds can reduce the reliance on expensive, synthetic antiviral drugs. While the uses of DEP are often discussed in the context of industrial applications (e.g., as plasticizers), emerging research suggests that DEP possesses antiviral properties. This ability makes DEP an attractive option for developing affordable antiviral therapies. One of the most significant advantages of using lemongrass-derived compounds, particularly DEP, is their low cost compared with pharmaceutical antiviral drugs. Lemongrass is easy to cultivate, widely available, and relatively inexpensive to process. This opens the door to developing antiviral treatments that could be accessible in low-resource settings or for treating emerging viral infections in areas where access to expensive pharmaceuticals is limited.

The use of lemongrass-derived antiviral compounds could be integrated into existing antiviral treatments, offering a complementary approach. For instance, these natural compounds could be combined with conventional antiviral drugs to enhance their effectiveness or reduce side effects, especially as part of a holistic or integrative health strategy. While the antiviral potential of lemongrass-derived diethyl phthalate is an exciting area of research, the reliance on in silico methods and the need for experimental validation highlight the current limitations. Overcoming these challenges through rigorous laboratory research, toxicity assessments, and clinical trials are essential before these compounds can be considered as viable antiviral therapies. As we explore the promising potential of lemongrass-derived compounds such as diethyl phthalate as cost-effective antiviral agents, we must recognize the importance of further experimental validation. Moving beyond computational predictions and in silico models, rigorous laboratory research, in vitro studies, and in vivo trials will be essential to confirm their efficacy, safety, and mechanisms of action. Only through these comprehensive investigations can we unlock the full therapeutic potential of these natural compounds and bring them to the forefront of antiviral treatment strategies. The future of antiviral therapies may may benefit from this exciting, sustainable approach, provided that scientific validation continues to guide its development.

4. CONCLUSIONS

Using Mpro as the target protein for SARS-CoV-2, several tests, including Lipinski's rule of five, molecular docking analysis, molecular dynamics simulations, and evaluation of chemical interactions, were conducted on the bioactive chemicals in lemongrass in this study. DEP is the finest ligand among all of them because molecular docking research and molecular dynamics simulations demonstrate its exceptional stability. It is advised that more studies be done, particularly pathway prediction using the database, and that in vitro and in vivo investigations be used to demonstrate the potential of DEP to determine the appropriate formula. Thus, lemongrass contains bioactive substances. The identification of the protein atoms and ligands that are bound can be analyzed to provide additional support for this investigation.

Author contributions: SA: Conceptualization, Writing-original draft, Data analysis, Data curation, Writing-review and Editing.

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Ethics statement: None.

Conflict of interest: No conflict of interest in this study.

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