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Original Article

Computer-Aided Drug Designing of Ocimum basilicum Compounds as Therapeutic Agents against RdRp of SARS-CoV2

Mehwish Shafiq[1], Rashid Saif[2*], Laraib Ali[1], Tuba Ahmad[3], Iram Anjum[1] and Anood Sohail[1]

[1]Department of Biotechnology, Kinnaird College for Women, Lahore, Pakistan
[2]Decode Genomics, Punjab University Employees Housing Scheme, Lahore, Pakistan
[3]Department of Biochemistry, Kinnaird College for Women, Lahore, Pakistan

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***Corresponding Author:**
Rashid Saif
Decode Genomics, 323-D, Punjab University Employees Housing Scheme, Lahore, Pakistan
rashid.saif37@gmail.com

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ABSTRACT

The prevailing situation of the World is challenging due to COVID-19 pandemic that is caused by SARS-CoV2. **Objectives:** To combat with this emerging pandemic by reducing disease severity and infection, the need of hour is to develop an effective vaccine and antiviral candidates as therapeutic agents against SARS-CoV2. **Methods:** This study was developed for the identification of potential anti-viral agents, from *Ocimum basilicum* against RdRp of SARS-CoV2. In this concern, nevadensin, ursolic acid, β-Sesquiphellandren, apigenin, nerolidol, nonyl acetate and geranyl acetate were screened out of fifty-seven compounds from *Ocimum basilicum* based on their best docking scores. The docking results were also compared with already clinically used drugs (Remdesivir and Ribavirin) against the RdRp of SARS-CoV2. Molecular docking was performed using MOE software. The ADMET analysis and drug likeliness were also performed for all screened compounds by using admetSAR, pkCSM and SwissADME. **Results:** Cumulatively, the optimum binding energies of screened compounds indicated their potential for drug development against SARS-CoV2. It appears promising that nevadensin exhibited a good docking score and high binding affinity towards RdRp of SARS-CoV2. Therefore, it may represent the potential to inhibit COVID-19. **Conclusion:** Hence, *Ocimum basilicum* nutraceuticals could be effective therapeutic candidates for the treatment and prevention of COVID-19.

INTRODUCTION

Coronavirus disease (COVID-19) is a communicable and life-threatening infection that is triggered by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV2) [1]. This virus is a single-stranded, positive-sense RNA enveloped and is transmissible in humans. The SARS-CoV2 belongs to MERS and SARS family; all of these are beta coronaviruses and they have their origins in bats. This viral infection was initially reported in Wuhan, China [2]. COVID-19 has subsequently spread internationally. On March 11, the World Health Organization (WHO) stated the 2019-2020 novel coronavirus as a pandemic [3]. COVID-19 causes a respiratory infection through common symptoms like cough, fever, difficulty in breathing, muscle pain, diarrhea, sore throat and sputum production are common symptoms [4]. However, the majority of COVID-19 cases lead to pneumonia, diarrhea along with multiple organ damage [5]. Among all organs of the body, the lungs are the most affected organ with COVID-19 due to the presence of enzyme ACE2 in the alveolar cells of lungs, and the SARA-CoV2 virus has an affinity with this enzyme on the receptor-binding site. Due to the progress of the alveolar disease, respiratory failure occurs as follows with the death of patients [6]. The SARS-CoV2 is a positive-sense, single-stranded RNA virus and its genome size varies from 29.8 to 29.9 kb [7]. The single virion (50-200 nanometer) comprises 4 different types of structural proteins. These

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structural proteins are identified as Spike protein (S), Envelope protein (E), Membrane protein (M) and Nucleocapsid protein(N). These proteins are different from one another with respect to structure as well as function; the N nucleocapsid protein holds the viral genome and other S, E, and M proteins are responsible for the formation of the viral envelope [8]. Spike proteins help in the attachment of the virion with the surface membrane of the host cell. Spike glycoproteins give the virus a corona-like appearance that is vital for its pathogenicity. The SARA-CoV2 virus has a suitable affinity with angiotensin-converting enzyme 2 (ACE2) present on the receptors of living cells that virion uses as a mechanism for entry into a cell [9]. Non-structural proteins occupy the two-third region of the genome of SARS-CoV2. Main proteases, RNA-Dependent RNA Polymerases and helicases are important non-structural proteins [10]. RNA-Dependent RNA Polymerases are coded by the nsp12 gene. It is an important multi-subunit enzymatic machinery in SARS-CoV2 that is involved in the replication and transcription processes in viral genomes [11]. Open reading frameworks ORF1a, ORF1b, and polyproteins(RdRp) along with nsp7 and nsp8 as cofactors are involved in RNA polymerization [12]. Catalytic domains and protein sequences of this enzyme are highly conserved, which could be a promising drug target for the development of a therapeutic approach against RdRp [13]. Natural compounds from Eastern herbs show active defense mechanisms against various pathogens. In modern phytomedicine, herbs and medicinal plants are used as an alternative therapy due to the presence of active chemical constituents against a wide variety of viruses. In this pandemic situation, there is a need for the development of effective antiviral drugs against COVID-19. In the present study, the computational approach is used for screening compounds from Ocimum basilicum (Sweet basil) to check their potentiality for blocking the RdRp proteins of SARS-CoV2. Computer-aided in silico approach helps to facilitate and speed up the drug designing process in which different methods are used to identify novel therapeutic compounds.

METHODS

Selection of medicinal plants for the discovery of potential antiviral drug agents was based on the presence of phytochemicals that are present in medicinal herbs. Here, we have selected the Ocimum basilicum which belongs to the Lamiaceae family. For a quite long time, it is being utilized in Asia as traditional medicine. It contains various compounds that have antiviral, antioxidant, antibacterial, antifungal, dermatologic, anticonvulsant and cytoprotective properties [14]. RdRp is a key enzyme in SARS-CoV2. RdRp non-structural protein (nsp12) belongs to the class of nucleic acid polymerases. It is a central component of enzymatic machinery that is involved in the replication and transcription of the viral genome of SARS-CoV2 [15]. So, by targeting RdRp, viral replication can be halted. The structure of target protein RdRp was obtained from the Protein Data Bank (PDB ID: 6M71). The structure of desired ligands was downloaded in SDF format from PubChem, Drug bank, ChEMBL and ChemSpider databases and sketched in the MOE interface by using Builder Mode. Canonical SMILES was used to build a 2D structure of ligands. After sketching the partial charges were added by using compute in MOE. Once charges were added, the prepared ligand was saved in the MDB file. PDB is a source of our target protein, which was downloaded in the 6M71 PDB file. For the preparation of protein following steps were performed: removal of inhibitors and repeated chains, correction of protein structure and 3D protonation of protein molecule. The repeated chains of RdRp were removed to avoid complications during docking. The molecular docking analysis was performed by Molecular Operating Environment (MOE) v.2015.10. (Developed by chemical computing group Inc, Canada). It was used to perform molecular docking for the protein-ligand interaction and drug-likeness analysis. MOE software was also used for the visualization of results, modeling, and simulation of structures. After molecular docking, virtually screened chemical compounds from Ocimum basilicum were selected as potential drug agents that have strong inhibitory effects against RdRp target protein by using Lipinski's rule and AdmetSAR profiling. Lipinski's rule is also known as the rule of five (RO5). The assessment of absorption, digestion, metabolism, excretion and toxicity (ADMET) of screened compounds is essential in the drug development process for the evaluation of drug-likeness, level of toxicity, and pharmacokinetics [16]. SwissADME, pkCSM and admetSAR are online web tools that were used for AdmetSAR profiling to evaluate the ADMET physiochemical properties, toxicity, pharmacokinetics and drug-likeness.

RESULTS

Molecular docking is an important tool to study interactions between protein and ligand at the atomic level. Here, we have investigated the binding efficiency of target protein RdRp of SARS-CoV2 with different ligands using a computational approach in order to predict promising therapeutic drug molecules. Target protein RdRp was docked with 57 different compounds of *Ocimum basilicum* (Figure 1).

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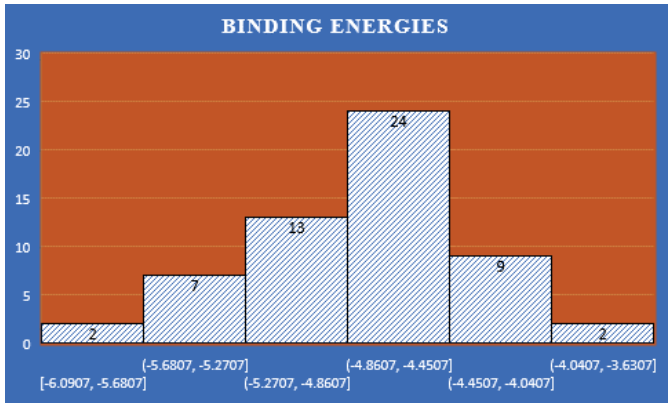


Figure 1. Histogram of molecular docking results of RdRp with several drug candidate compounds; x-axis: binding energies ΔG in kcal/mol; y-axis: number of compounds

After comprehensive analysis and comparison of the docking results of all compounds with control drugs, we have selected seven compounds of *Ocimum basilicum* based on their docking scores and molecular interactions of protein-ligand complexes (Table 1).

Compounds	Docking Scores (Kcal/mol)
Nevadensin	-6.0907
Ursolic acid	-5.9506
β- Sesquiphellandren	-5.6538
Apigenin	-5.6119
Nerolidol	-5.5728
Nonyl acetate	-5.5153
Geranyl acetate	-5.4095

Table 1: Docking scores of selected compounds of Ocimum basilicum with target protein (PDB ID:6M71)

Docking results ranked by binding energy (ΔG) values of different ligands are: nevadensin > ursolic acid > β-Sesquiphellandren > apigenin > nerolidol > nonyl acetate > geranyl acetate with binding energies -6.09, -5.95, -5.65, -5.61, -5.57, -5.51 and -5.40 kcal/mol, respectively (Figure 2).

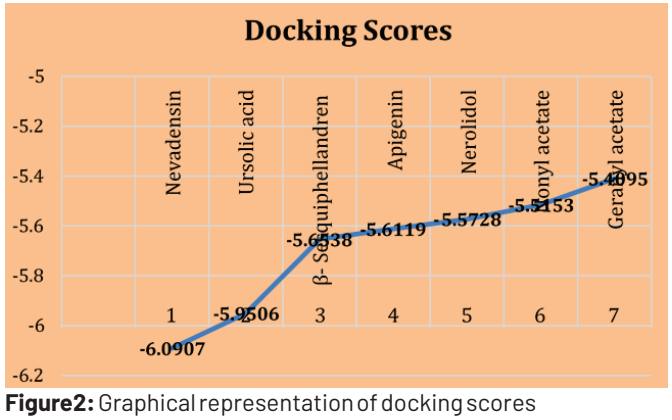


Figure2: Graphical representation of docking scores

Concerning docking analysis, nevadensin expressed high binding affinity towards RdRp polymerase of SARS-CoV2 than standard ribavirin drug -6.09, -5.38 kcal/mol, respectively (Table 2).

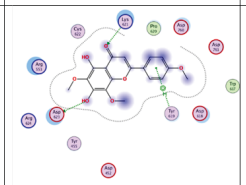
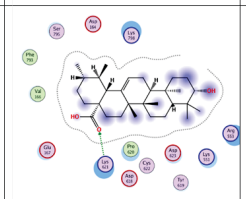
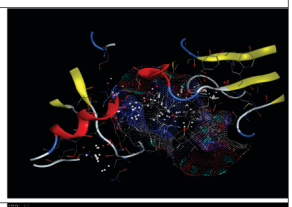
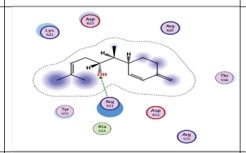
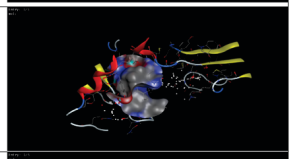
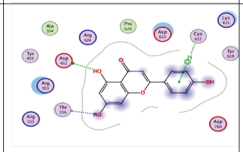
Names and Possible Interactions	2D Interactions	3D Structures
Nevadensin LYS-621 (H-acceptor) ASP-623 (H-donor) TYR-619 (π-H)		
Ursolic acid LYS-621 (H-acceptor)		
β-Sesquiphellandren ARG-553 (H-acceptor)		
Apigenin THR-556 (H-acceptor) ASP-452 (H-donor) CYS-622 (π-H)		

Table 2: 2D interactions and 3D structures of selected protein-ligand complexes

Virtually screened chemical compounds from Ocimum basilicum were selected as potential drug agents that have strong inhibitory effects against RdRp target protein by using Lipinski's rule and AdmetSAR profiling. (Table 3).

Ligands	MW (g/mol) (≤500)	Donor HB (≤5)	Acceptor HB (≤10)	TPSA (Å)	Log P	Log S	Violation
Nevadensin	344.32	2	7	98.36 Å^2	2.90	-4.03	0
Ursolic acid	456.70	2	3	57.53 Å^2	7.09	-4.38	1
β- Sesquiphellandren	220.35	1	1	20.23 Å^2	3.86	-3.62	0
Apigenin	270.24	3	5	90.90 Å^2	2.58	-2.77	0
Nerolidol	222.37	1	1	20.23 Å^2	4.40	-3.80	0
Nonyl acetate	186.29	0	2	26.30 Å^2	3.30	-2.86	0
Geranyl acetate	196.28	0	2	26.30 Å^2	3.24	-3.21	0

Table 3: AdmetSAR profiling of Ocimum basilicum compounds according to Lipinski's rule of five

The drug likeliness properties of all selected compounds' molecular weight range from 186.29 to 344.32 < 500 Daltons. Besides, number of hydrogen bond donors (NH and OH) less than 5 and numbers of hydrogen bond acceptors (O and N) less than 10 were predicated in all selected compounds (table 4).

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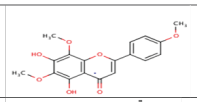
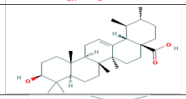
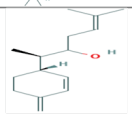
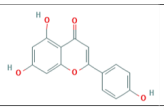
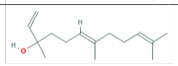
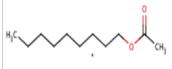
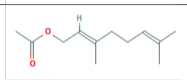
Ligands	Hit Structure	Bioavailability score	Synthetic accessibility score
ChEBI ID: 7545 Nevadensin		0.55	3.47
Pub Chem CID: 64945 Ursolic acid		0.85	6.21
Pub Chem CID: 91749844 β-Sesquiphellandren		0.55	4.43
Pub Chem CID: 5280443 Apigenin		0.55	2.96
Pub Chem CID: 5284507 Nerolidol		0.55	3.53
ChEBI ID: 87511 Nonyl acetate		0.55	1.92
Pub Chem CID: 1549026 Geranyl acetate		0.55	2.72

Table 4: Bioavailability and synthetic accessibility scores of top screened molecules

DISCUSSION

In silico methods, such as molecular docking, are frequently used to analyse the interactions and binding affinity of proteins and peptides in biological activity. Unfortunately, limited sampling of both ligand and receptor conformations, as well as the use of estimated scoring systems, might result in results that do not correspond to actual experimental binding affinities. Molecular dynamics simulations (MDS) can provide useful information in decoding functional processes of proteins/peptides and other biomolecules, circumventing the stringent sampling constraints of docking research [17]. Docking results ranked by binding energy (ΔG) values of different ligands are: nevadensin > ursolic acid > β-Sesquiphellandren > apigenin > nerolidol > nonyl acetate > geranyl acetate with binding energies -6.09, -5.95, -5.65, -5.61, -5.57, -5.51 and -5.40 kcal/mol, respectively. A significant issue in medication design is obtaining molecules that bind selectively to their target receptors while without causing side effects by attaching to other similar receptors. We examine techniques for addressing this problem using COMBINE (COMparative BINding Energy) analysis in conjunction with PIPSA (Protein Interaction Property Similarity Analysis) and ligand docking approaches. We put these approaches to the test by using different sets of inhibitors of three structurally related serine proteases of medicinal importance [18]. In this study virtually screened chemical compounds from *Ocimum basilicum* were selected as potential drug agents that have strong inhibitory effects against RdRp target protein by using Lipinski's rule and AdmetSAR profiling. In the drug discovery process, bioavailability prediction and pharmacokinetics parameters are very important [19]. Permeability possessions (log P) value less than 5 of all compounds were also studied except ursolic acid with 7.09 log P and Topological Polar Surface Area (TPSA) of all ligands were less than 140 $Å^2$. It is an important component in computer-aided drug designing [20].

CONCLUSIONS

The current study has provided a computer-aided drug designing (CADD) approach for potential drug agents from *Ocimum basilicum* against SARS-CoV2. The aim of this study was to examine the compounds of *Ocimum basilicum* against viral protein RdRp of SARS-CoV2, which is essential for viral replication. The main target protein RdRp was used to predict its molecular binding and docking score with different ligands of the selected plant. Therefore, the major seven compounds from *Ocimum basilicum* which gave the best lowest binding energies were selected. It appears promising that nevadensin exhibited a good docking score and high binding affinity with RdRp of SARS-CoV2. Hence, it may have the potential to inhibit COVID-19. Additionally, ursolic acid, β-Sesquiphellandren, apigenin, nerolidol, nonyl acetates and geranyl acetate seems to have the best potential to act as polymerase inhibitors of SARS-CoV2. Thus, these suggested therapeutic candidates as COVID-19 polymerase inhibitors need further investigations and clinical trials for their potential medicinal uses against SARS-CoV2.

Conflicts of Interest

The authors declare no conflict of interest

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