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Computational Prediction of *Olea europaea* Compounds as Inhibitor of Main-Peptidase of SARS-CoV2

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Abstract

Background: In December 2019, Severe Acute Respiratory Syndrome Novel Coronavirus 2 (SARS-nCOV2) was identified as potential causative agent for COVID-19 in the Wuhan City of China. This disease spread around the whole globe, thus WHO declared it as a pandemic by March 11, 2020. Due to rapid mutation rate, lack of specific genomic knowledge and treatment modalities against this RNA based virus, world scientific community urges to work for vaccine production, treatments options and alternative remedies including eastern herbs as potential anti-viral agents.

Methods: *Olea europaea* (Olive) was found highly beneficial on the basis of its previous therapeutic applications. So, in the current study, its five different compounds (*Catechin, Cynaroside, Elenolic Acid, Hydroxytyrosol,* and *Oleuropein*) were chosen according to Lipinski physiochemical parameters, which were compared with already clinically used five anti-viral drugs (*Ribavirin, Niclosamide, Nelfinavir, S-Nitroso-N-acetyl penicillamine, Chloroquine*) against the Main-Peptidase (PDB ID:2GTB) of SARS-nCoV2 using Molecular Operating Environment (MOE) software.

Results: Among the chosen compounds of *Olea europaea* which were docked on the active site of Main-Peptidase, Oleuropein provide the best minimum binding energy of -8.3201kcal/mol followed by Cynaroside with -7.2121kcal/mol. These two energy complexes are considered to have better drug potential in this initial studies as compare to the already commercially used drug agents e.g. *Chloroquine, Ribavirin, Niclosamide and S-Nitroso-N-acetyl Penicillamine* having binding energy of -6.7168, -5.8171, -6.3361 and -5.4219kcal/mol respectively. Other three agents from olive were also docked to compare the binding energy of aforementioned clinically used drugs.

Conclusion: Oleuropein and Cynaroside are considered to be the most compelling compounds as a drug agent against coronavirus2 infection. Further, molecular dynamic simulations and in-vivo investigations are needed to endorse the current findings of these compounds as potential drugs.

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Introduction

Rapid outbreak of respiratory disease in China caused nearly 1,016,395 worldwide deaths which posed serious public health issue [1]. Then in December 2019, Center for Disease Control and Prevention (CDC), Atlanta investigated and confirmed that a novel disease like pneumonia was caused by a novel coronavirus which was later, named SARS-nCoV2. This virus outbreak was originated in Wuhan city [2]. Due to its transmissible characteristics, it spread across 216 countries and territories around the world have reported 49,035,014 confirmed cases of the coronavirus globally. On March 11, WHO declared it as a pandemic disease. Then efforts were begun to find a productive treatment against Coronavirus Disease 2019 (COVID-19). Even after lots of efforts, no effective drugs were found, so scientists moved on to some natural herbs that have been used as traditional remedies since centuries. So, *Olea europaea* (Olive) plants was chosen here as a traditional remedy to check its efficacy against novel coronavirus, which have remarkable compounds named Catechin, Cynaroside, Oleuropein, Elenolic acid and Hydroxytyrosol. They have diversity of crucial therapeutic benefits such as antioxidant [3], cardio protective [4] and hypoglycaemic effect [5]. Previous investigations reported the therapeutic effects of *Olea europaea* against SARS-nCoV2 and provide clues for further investigations on other herbs such as *Nigella sativa* which is also considered effective against SARS-nCoV2 [6]. Molecular docking of *Olea europaea* compounds were done against Main-Peptidase protein of coronavirus2 (PDB ID: 2GTB) and also compared with commercially used anti-viral drugs to check the drug efficacy of olive compounds against the COVID-19 spread. This study was performed by Molecular Operating Environment (MOE) software [7].

Methods

Potential drug agents and target protein retrieval

Olea europaea was studied as a curative herb choice and its selected compounds such as Cynaroside, Elenolic Acid, Hydroxytyrosol, Catechin and Oleuropein retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/) (Fig. 1), that were also reviewed from the literature according to Lipinski's physiochemical parameters (Table 1) [8,9] to predict their drug potential properties. Their 3D structures were prepared by using ChemDraw 7.0.3. Similarly, selected target protein is the Main Peptidase of SARS-nCoV2 as it plays an essential role in the synthesis of RNA dependent RNA polymerase and helicase due to which it acts as an attractive and potential target for molecular docking [10]. The structure of Main Peptidase was obtained from Protein Data Bank (PDB) (https://www.rcsb.org/). Other clinically used drugs were also selected according to Lipinski's rule of five and their chemical structure are shown (Fig. 2, Table 2) [11,12].

Molecular Operating Environment (MOE) software

The molecular docking analysis was performed by MOE software v.2015.10. [7] to obtain binding energies scores of the complexes. MOE searches the best binding sites between the ligand and targeted macromolecules in 3D docking boxes [13]. All the parameters were performed by default application on 64GB with 5 core CPUs in Windows 10 Operating System.

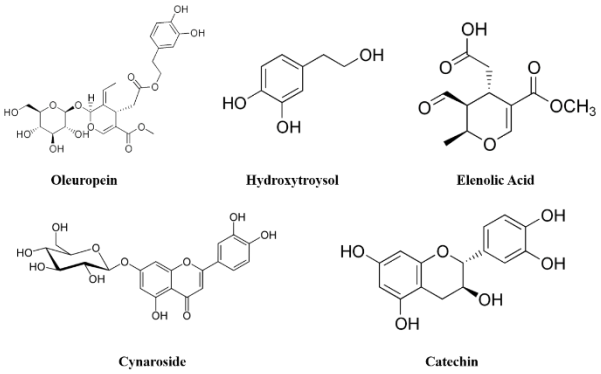

Figure 1: Chemical structure of five selected *Olea europaea* compounds.

Ligand	Molecular Weight (g/mol)	H-Donor	H-Acceptor	TPSA (Å)	Log P
Catechin	290.27 g/mol	5	6	110	0.4
Cynaroside	488.4 g/mol	7	11	186	0.5
Elenolic Acid	242 g/mol	1	6	89.9	0.4
Hydroxytyrosol	154.1 g/mol	3	3	60.7	-0.7
Oleuropein	5404.4 g/mol	6	13	202	-0.4

Table 1: Physiological properties of compounds of *Olea europaea* according to Lipinski's Rule.

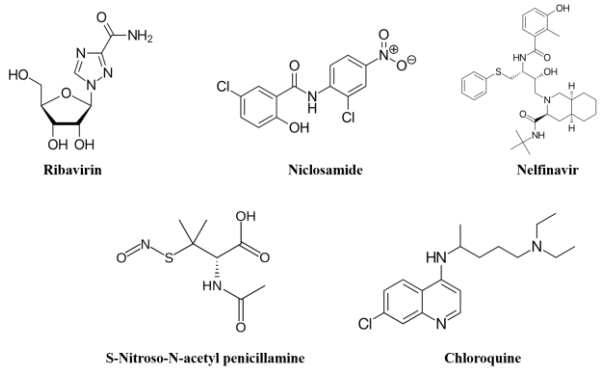

Figure 2: Chemical structure of five commercial anti-viral drugs.

Name	Molecular Weight (g/mol)	H-Donor	H-Acceptor	Log P	TPSA (Å)	H-atom count
Ribavirin	244.2 g/mol	4	7	-1.8	144	17
Niclosamide	327.12 g/mol	2	4	4	95.21	21
Nelfinavir	567.8 g/mol	4	6	5.7	127	40
S-Nitroso-N acetyl penicillamine	220.25 g/mol	2	6	-0.3	121	14
Chloroquine	319.9 g/mol	1	3	4.6	28.2	22

Table 2: Properties of clinically used anti-viral drugs according to Lipinski's rule of five.

Protein/Enzyme	PDB ID	Classification	Organism	Resolution	Detection Method	Mol. Weight (DA)	Chain
Main-Peptidase	2GTB	Hydrolase	SARS-nCoV2	2Å	X-ray diffraction	34694.48	A

Table 3: Crystalline properties of the Main-Peptidase protein of coronavirus.

Preparation of ligand

The structure of Cynaroside and other compounds were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) database. Ligand was prepared by MOE using canonical structure. Partial charges on the ligand molecule were applied and saved in .mdb format.

Preparation of protein

The structure of the Main-Peptidase cleavage protein of coronavirus was retrieved from PDB. Crystalline properties of the selected protein are mentioned in (Table 3). For the preparation, the sequence of a protein was edited to remove the water molecules and other ligand attached to the protein.

3D Protonation of protein

3D protonation is the inclusion of proton into a molecule, atom and ion. Although, 3D protonation changes the charges of the molecule up to one unit but some time it is unaffected during hydrogenation. 3D protonation exists in a wide variety of catalytic reactions that's why 3D protonation before molecular docking was used because certain residues and small molecules would be ionized under experimental conditions. Main-Peptidase protein molecule was prepared by 3D protonation while other factors such as temperature, pH, and salt remained constant according to the software default settings.

Identifications of protein active site

An active site or binding pocket of a protein is identified by the Site Finder tool of MOE software [14]. This method is energy-based for the prediction of active sites of a protein molecule.

Molecular docking run

Ligand-protein run was performed by MOE after preparation of our ligand and protein molecules. For docking run, select the Dock option, run the docking process by keeping all other parameters constant, then select the dummy atom from the site and choose .mdb ligand file. After successful docking of proteins and all compounds, their 2D & 3D interactions and binding energies were calculated.

Results

Main-Peptidase protein of SARS-nCoV2 was docked with five different compounds (Catechin, Cynaroside, Elenolic Acid, Hydroxytyrosol, Oleuropein) of *Olea europaea.* The target protein was prepared by 3D protonation and then used as a template for docking. The main active sites of protein residue were identified by the Site Finder feature of MOE software e.g. THR2, THR26, LEU27, HIS41, CYS44, MET49, PRO52, TYR54, PHE140. Different binding energies/docking score and root-mean-square deviation (RMSD) values of the complexes are determined which show the interaction potential, stability of our complexes and average distance between the atoms of our targeted protein respectively (Table 4).

The data from binding energies showed that the compounds of *Olea europaea* have some very promising energy complexes, for instance, two of our tested *Oleuropein* and *Cynaroside* complexes with our targeted protein of Main-Peptidase gave the energy values of -8.3201 and -7.2121 Kcal/mol which are even better than the energy values of clinically used anti-viral drugs of *Niclosamide*, *Chloroquine*, *Ribavirin* and *Nelfinavir* with -6.3361, -6.1768, -5.8171 and -5.4219Kcal/mol respectively. Similarly, our other two tested complexes of *Catechin* and *Elenolic Acid* gave -6.0237 and -5.4360 Kcal/mol energies which are better than clinically used anti-viral drugs of *Ribavirin* and *S-Nitroso-N-acetyl penicillamine* with -5.8171 and -5.4219Kcal/mol energies respectively. Docking scores of our five tested complexes and their comparison with clinically used drugs are given in (Table 5).

Compounds	Docking Score	RMSD Value
Oleuropein	-8.3201	2.5832
Cynaroside	-7.2121	1.5454
Catechin	-6.0237	3.3014
Elenolic Acid	-5.4360	1.3060
Hydroxytyrosol	-4.5463	0.9260

Table 4: Docking score of *Olea europaea* compounds with target protein.

Olea europaea Compounds	Score	Already used Drugs	Score
Oleuropein	-8.3201	Nelfinavir	-8.4625
Cynaroside	-7.2121	Niclosamide	-6.3361
Catechin	-6.0237	Chloroquine	-6.1768
Elenolic Acid	-5.4360	Ribavirin	-5.8171
Hydroxytyrosol	-4.5463	S-Nitroso-N-acetyl penicillamine	-5.4219

Table 5: Comparison between clinically used drugs and compounds of *Olea europaea.*

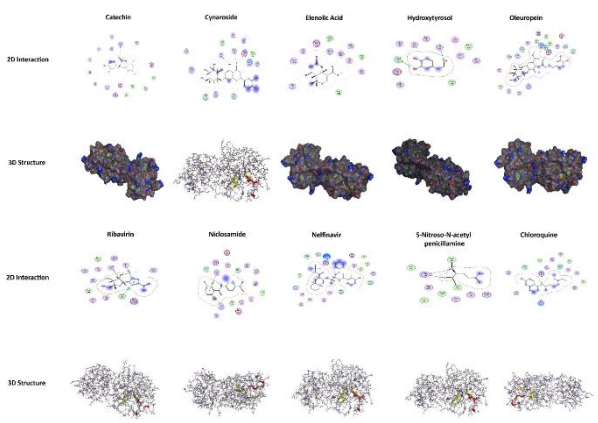

Figure 3: 2-Dimensional & 3-Dimensional structure complexes of five compounds from Olea Europaea and five other clinically used anti-viral drugs.

Discussion

COVID-19 has affected the human population all around the world and appeared as great threat to global health. Although, there is no drug/vaccine has been accepted till date but endeavours are being made in different domains of medicines including allopathic, homeopathic, herbal and biologics fields. Plants are considered to be one of the great reservoirs for searching potential drug agents during this era of current pandemic [15]. So, *Olea europaea* plant was chosen to study as a potential drug

against this infection. Various aforementioned compounds of *Olea europaea* were selected according to the Lipinski's physiochemical properties and they were docked with the Main-Peptidase of coronavirus by using MOE Software. Secondly, aforementioned clinically used drug agents were also docked to Main-Peptidase of coronavirus. The obtained scores were compared with clinically used anti-viral drugs which showed very promising results and this plant have the potential to serve as a first shield against corona virus infections until the production, efficacy and acceptance of its potential vaccine.

Our results are endorsed with many of the previous studies where olive compounds are beneficial in many diseases including COVID-19 [16-18]. This hypothesis still needs further molecular dynamic simulations studies and in-vivo animal and human trials for validation against the existing peril of COVID-19.

Purpose of this study is to check the inhibitory effects of the *Olea europaea* compounds as drug agent with therapeutic effects on the Main-Peptidase of SARS-nCoV2. We found that *Oleuropein* and *Cynaroside* have the lowest energy binding complex as compared to marketed anti-viral drug agents. Therefore, we assume that usage of olive which contains *Oleuropein* and *Cynaroside* may help to reduce the infection of SARS-nCoV2. However, further *in-vitro* and *in-vivo* studies are still needed to validate this hypothesis which is postulated through this initial computer aided prediction of aforementioned compounds as potential drug.

Author Contributions

Rashid Saif (RS) envisage the research idea, analyse the data and proof read the manuscript. Ghafran Ali (GA) & Kanza Ashfaq (KA) helped in data analysis and in initial write-up of the manuscript. Saeeda Zia (SZ) helped in data analysis and to further understand the mathematics behind the docking methods. Abdul Rasheed Qureshi (ARQ) helped in to design the project and proof reading of the manuscript.

Competing Interest

All authors declare no conflicts of interest in this paper.

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