An Old Adult with Alzheimer's Disease and Dementia Represented Reduced COVID-19 Symptoms, Probably Due to Cross Impact of Drugs; A Case-Report Blended with Computational Biology Study

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Abstract

Background

Studies have shown that morbidity and mortality critically increase from COVID-19 in patients with Alzheimer's disease and dementia. But we had an Alzheimer's disease patient treated rapidly from COVID-19 involvement. We explore the probable cause of treatment using in-silico drug screening tools.

Case presentation

We present an 81-year-old female patient who recovered from COVID-19 disease despite her severe dementia and Alzheimer's disease, and unfavorable respiratory status. The patient was under medical care for ten days. She received standard COVID-19 medical care plus her drugs for Alzheimer's disease. We found those drugs administered for Alzheimer's disease can interact, and probably inhibit, SARS-COV-2 main protease that plays a central role in virus replication.

Conclusion

Our patient remediated from COVID-19 very well despite being at a higher risk of morbidity and mortality. However, her amnesia may help her to fight and resist respiratory distress. In addition, administered drugs for Alzheimer's disease may interact with viral biomolecules and dwindle SARS-COV-2 replication.

Keywords: Dementia, Cognition, Alzheimer's Disease, COVID-19.

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Background

COVID-19 or SARS-CoV-2 reported from China in December 2019. World Health Organization first presented it as unusual pneumonia without any known reason, leading to a pandemic, and declared a major health crisis affecting all nations worldwide on March 11, 2020 (1-3). Several reports have shown that most patients with dementia have a higher risk of contracting SARS-CoV-2, especially ones over 65 years (4, 5). Moreover, morbidity and mortality rates of COVID-19 are increased critically in patients with dementia and senile ones (4-6). About 33 percent of people over age 70 years have cognition problems or mild dementia. Also, fifty million people in the world live with dementia approximately (6-8).

In this case report, we have presented clinical and paraclinical features of an 81 years old female suffering from Alzheimer's disease who was admitted to the ICU and cured after ten days of hospitalization. In addition, we have done a bioinformatics study on the patient medications to

evaluate a probable cause of COVID-19 remediation in a patient with Alzheimer's disease. Using a drug screening approach, we studied the potential inhibitory effect of administered drugs for Alzheimer's disease on a master protein of SARS-CoV-2. We think such an approach helps physicians apply personalized medicine using bioinformatics tools in a new way we presented in this report.

Case presentation

The patient was an 81-year-old female with a past medical history of Alzheimer's disease, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, and ischemic heart disease. We admitted her with severe dry cough and dyspnea five days before hospitalization, and her fever arose on her admission day. Due to a history of hypertension and diabetes, the patient was treated and controlled with Amlodipine 5 mg/bid, valsartan 80 mg/bid, and Metformin 500 mg/tid. The patient and his family had no history of drug or food allergies. She had not a vaccination history against COVID-19 disease. Her blood pressure was 150/80 mmHg, pulse rate of 88/min, respiratory rate of 28 breaths/minute, the body temperature of 38.9°C, and SPO2 was 75% without supportive oxygen.

Laboratory findings included CRP: 60.5 mg/l, AST: 39 U/L, ALT: 35 U/L, Urea: 52mg/dl, Cr:0.85 mg/dl, PT: 23 secs, INR: 2.6, PTT: 38.5 secs, WBC count: 10000 cells/µL, Neutrophil percent: 83%, Lymphocyte percent: 14%, hemoglobin: 12.8 gm/dL, Platelet count: 285000 cells/µL), vitamin D3 serum level: 86 ng/ml, D-dimer: negative, negative procalcitonin and normal venous blood gas (VBG). Her CT scan showed patchy infiltration on both lungs, presented on peripheral parts of the lungs (**Figure 1**).

Therefore, she was admitted to the ICU because of low SPO2. RT-PCR test on a pharyngeal specimen confirmed the diagnosis of COVID-19. Consequently, her treatment was provided with five days of azithromycin and prednisolone 5 mg/day. Her oxygenation was started with a face mask with a reservoir for two days and changed to a face mask after three days and a nasal cannula. We administered daily Pulmicort nebulizer for her, in addition to well hydration and nutrition supplements like vitamin C in a dose of 1 gm/day and Zinc in combination with her drugs like Amlodipine 5 mg/bid, valsartan 80 mg/bid, Memantine 5 mg/day, Citalopram 20 mg/day, Aspirin 80 mg/day, Depakin 250 mg/bid, Donepezil 10 mg/day, Pancreatin daily, and Clonazepam 1 mg/day.

After the next seven days of hospitalization, on discharge day from ICU (day 10), she had a white blood cell count: 5900 cells/µL (Lymphocyte%: 65%, Neutrophil%.: 28%), CRP: 14.5 mg/L. After ten days of treatment, she was discharged from the hospital with SPo2: 98%, without supportive oxygen, and no other symptoms. This quick response to treatment was a medical miracle in her age and comorbidities. We expected a longer time of hospitalization for this case with severe outcomes.

Drug screening approach to elucidation probable mechanism of fast remediation from COVID-19 in our case

We did a docking study to respond to the question of whether prescribed drugs for alleviating Alzheimer's disease can be potent interactive ligands for COVID-19 main protease enzyme (3CL pro). Hence, we have done a docking study using an in-silico drug screening tool. We obtained a three-dimensional structure (SDF format) of chemical compounds from the ZINC Docking repository (9) (**Table 1**). The drugs included Aspirin, Donepezil, Depakin, Citalopram, Memantine, Clonazepam, Diovan, and Amlodipine. We downloaded the tertiary structure (3D) of COVID-19 main protease from the protein data bank (PDB) repository [PDB code 6LU7]. This structure is expressed in Escherichia coli BL21(DE3) system and visualized using the X-Ray diffraction method (resolution: 2.16 Å) (10). Anyhow, during the crystallography process, the authors have used an inhibitor known as "N-[(5-METHYLISOXAZOL-3-YL) CARBONYL] ALANYL-L-VALYL-N~1~-((1R,2Z)-4-(BENZYLOXY)-4-OXO-1-{[(3R)-2-OXOPYRROLIDIN-3-YL]METHYL}BUT-2-ENYL)-L-LEUCINAMIDE" (Leucinamide). We have considered the Leucinamide, as the reference ligand.

We have used Molegro Virtual Docker (MVD) Ver.6 (Molexus IVS, Denmark) for the docking study. We have installed MVD on an HP G62 Notebook PC equipped with a 64-bit Windows operating system, Intel(R) Core(TM) i3 CPU processor, and 6 GHz RAM. We interacted with SDF formats of drugs with protein 3D-structure of COVID-19 main protease, without water molecules. We selected 0.3 Å grid space for calculations, the energy minimization, and optimization of hydrogen bonds. MVD results were as the MolDoc scores that are a function of calculated ligand-receptor (protein) interaction energy; the more negative scores mean better binding potency. Figure 2 depicts a view of ligand-protein docking in MVD software in our work.

Nine evaluated ligands interacted with 166 poses of COVID-19 main protease. The binding pocket of interest was the inhibition site of the Leucinamide molecule. We transferred MolDock scores to SPSS ver.20 software. Using one-way analysis of variances (ANOVA), we compared MolDock scores to find out the best interactive ligand.

Discussion and Conclusion

We have reported 81-year-old female suffering from Alzheimer's disease for nine years who was recently infected with SARS-COV2. Alzheimer's disease is one of the risk factors for COVID-19 mortality. It is hard to teach an Alzheimer's disease patient how to wear the mask and

apply other sanitary protocols because of cognitive problems. Consequently, this situation leads to disease progression (5).

Although our case was under the same medication, like other Alzheimer's patients, she experienced milder illness with fewer exacerbation periods and relatively faster remission. This case led us to focus on the potential causes of shorter remediation time and milder symptoms of COVID-19. Hence, we did a virtual analysis on the interaction of Alzheimer's disease medications with SARS-COV-2 main protease, known as 3CL pro, a key enzyme in coronavirus replication.

A previous report has noted that older people with dementia and COVID-19 may have mild and unusual symptoms (6). Moreover, it has been shown that a decrease in angiotensin-converting enzyme-2 (ACE2) activity in people with Alzheimer's disease with COVID-19 may play a role in shortening the hospitalization time of these patients (7, 8).

Another possible explanation would be that as dementia patients develop different degrees of apathy mainly to environmental changes (11), they would not like a patient with routine disease status (as far as dementia is concerned) to their hospitalization and different applied treatments. Physiologically, complete awareness of these serious conditions results in moderate to severe psychological stress and anxiety. Consequently, the chronic phase of Alzheimer's disease may reduce the immune system's efficacy in forcefully eradicating the pathogen. Finally, this may cause deterioration of the patient's health condition (12). However, due to progressive apathy in dementia patients, their awareness of the status and environment is diminished meaningfully. Thus, our case may be under mild levels of psychological stress and anxiety (11), and as a result, this helps her to maintain his emotional stability and high-performance immune responses. In this regard, a report has mentioned that people with Alzheimer's disease and carrying APOE4 had fewer chronic disease experiences, and it may help patients with COVID-19 accelerate the healing process (13). It seems that the disability of our case to remember the recent information about a newly rising contagious disease with high morbidity and mortality rates plus proper and timely treatment management can be responsible for her emotional and psychological stability during her hospitalization period.

Presented case with severe dementia and Alzheimer's disease recovered early from COVID-19 while she had a higher risk for its mortality. Further investigations are needed to perform on other dementia patients with COVID-19 disease.

Another issue is the anti-inflammatory effect of drugs used for this Alzheimer's patient. Inflammation is fundamental for COVID-19 involvement outcomes that dwindled in our case, probably because of the immune-suppressive impacts of anti-Alzheimer drugs. Anyhow, this declaration should be confirmed using clinical data and research.

Docking results findings

We have presented docking results, by descending order of mean±sd DOS value, in **Table 2**; from nine ligands, the best score belongs to the reference one (Leucinamide), followed by Diovan, Citalopram, Amlodipine, Donepezil, Clonazepam, Aspirin, Depakin, Memantine, respectively. There was a significant difference between DOS (CI= 0.95; p= 0.000) when compared ligands by the one-way ANOVA statistical method. Leucinamide was considerably different from all other investigated ligands (p= 0.000). Other molecules also had significant p-values when compared to each other using Tukey posthoc method, except in some cases. DOS of Aspirin was like DOS of Depakin (p= 1.000) or Memantine (p= 0.121). DOS of Donepezil was like DOS of Clonazepam (p= 1.000), Citalopram (p= 0.075), and Amlodipine (p= 0.774). DOS of Depakin was like DOS of Memantine (p= 0.121). DOS of Citalopram was like DOS of Amlodipine (p= 0.974). DOS of Memantine was like DOS of Depakin (p= 0.121). DOS of Clonazepam was like DOS of Amlodipine (p= 0.506). All other comparisons between the two drug sets were significantly different (p= 0.000 or $p< 0.05$; details not shown).

Diovan only targeted 12 positions on COVID-19 main protease, but it was the best drug amongst others because its DOS mean±sd= 117.37±11.51 and minimum DOS= -135.80. Contrary, Memantine fulfilled the most positions (29 poses) than others but with the weakest DOS (mean±sd DOS= -52.71±11.71; minimum DOS= -75.29). Anyhow, all tested ligands targeted the COVID-19 main protease, effectively and with negative DOS. DOS is a function of Gibs free energy (ΔG) calculated during docking study at the active site of ligand-receptor (protein) molecules. Note that the more negative scores (or ΔG) mean better binding potency and probably inhibition of the protein. Therefore, all eight administered drugs are expected to interact with COVID-19 main protease and can alleviate viral replication. **Figures 3** to **7** represent graphical docking results for each evaluated drug, hydrogen bonds formed between drug and targeted amino acid in 3CL pro structure. Leucinamide and Amlodipine targeted both Phe 140 and Glu 166; therefore, these two amino acids could be good hot points for blocking SARS-COV-2 replication. Collectively, we can propose that Amlodipine may exert its anti-SARS-COV-2 activity via inhibition of 3CL pro like the known inhibitor, the Leucinamide. In our work, Leucinamide was the reference ligand. **Figure 8** depicts a comparative box-plot for mean±sd of DOS of studied chemicals; it is obvious that Leucinamide has the best score (more negative is better) than others, followed by Diovan, Citalopram, Amlodipine, Donepezil, Clonazepam, Aspirin, Depakin, Memantine, respectively.

The drug screening approach confirms that drugs administered for controlling Alzheimer's disease, in our case, can inhibit the 3CL pro enzyme of SARS-COV-2. Therefore, we think that fast remediation from COVID-19 symptoms is an outcome of administered drugs, especially that with better DOS, such as Diovan, Citalopram, and Amlodipine, in addition to other five medications. A brief view of the probable mechanism of SARS-COV-2 inhibition by administered drugs for our case is represented in **Figure 9**.

Considering our approach in this study, we suggest that bioinformatics tools and special drug screening tools give physicians a better point of view about the cross-effect of a drug in two different diseases with different mechanisms and physiopathology. It is worthful in personalized medicine and finding new treatments using currently approved drug formulas. We suggest investigators test our approach in their current and future works.

Consent for publication

Written informed consent was obtained from the patient next of kin for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Abbreviation list

ACE: angiotensin converting enzyme; ALT: Alanine Transaminase; APOE4: Apolipoprotein E-4; AST: Aspartate Transaminase; CBC: Complete Blood Count; COVID-19: Coronavirus disease 2019; Cr: Creatinine; CRP: C-Reactive Protein; CT: computerized tomography DOS: Docking score; Lymph: Lymphocyte; Hg: Hemoglobin; ICU: Intensive Care Unit; INR: International Normalized ratio; Neut: Neutrophil; PT: Prothrombin Time; PTT: Partial Thromboplastin Time; Plt: Platelet; RT-PCR: Reverse Transcriptase Polymerase Chain Reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; VBG: Venous Blood Gas; WBC: white blood cells.

Declarations

Ethics approval and consent to participate: All the ethical considerations based on the international ethical protocols were considered by the authors and the work was approved by the ethics committee of Laleh hospital in Tehran city.

Availability of Data and Materials

The information in this manuscript was collected from the corona ward of Laleh Hospital in Tehran. All data generated or analyzed during this study are gathered in this manuscript.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors Contributions

MT, MA, and PH analyzed and interpreted the patient data regarding Alzheimer's disease. AL and AH performed the physical examination and were major contributors to writing the manuscript. All authors read and approved the final manuscript**.** MT done in silico and bioinformatics analysis.

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Table 1: Chemical components structures, Zinc code and traditional names of drugs used for presented case-report with Alzheimer's disease

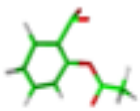
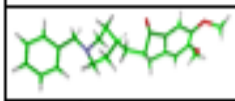
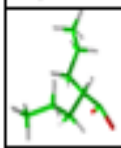
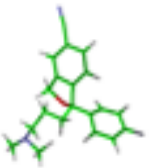
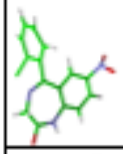
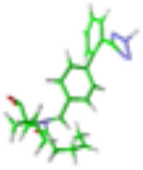
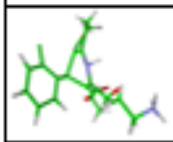
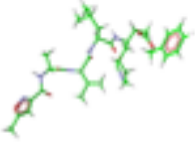
Structure and Zinc Code	Approved for/as
 ZINC000000000053-Aspirin	Anti-inflammatory
 ZINC000000597013-Donepezil	dementia of the Alzheimer's type
 ZINC000003008621-Depakin (Sodium valproate)	Epilepsy, bipolar disorder, migraine headaches, prevention of seizures
 ZINC000003794601-Citalopram	antidepressant (selective serotonin reuptake inhibitor class), major depressive disorder, obsessive compulsive disorder, panic disorder, and social phobia
 ZINC000003812933-Memantine	to slow the progression of moderate-to-severe Alzheimer's disease
 ZINC000003813003-Clonazepam	to prevent and treat seizures, panic disorder, anxiety, and the movement disorder known as akathisia
 ZINC000003875259-Diovan (Valsartan)	to treat high blood pressure, heart failure, and diabetic kidney disease
 ZINC000100001964-Amlodipine	calcium channel blocker; to treat high blood pressure and coronary artery disease
 Reference ligand: Leucinamide	inhibitor N3;used for crystalography of COVID-19 main protease enzyme

Table 2: Docking scores, counts of docked poses, Mean±Sd of docking scores, the best/the weakest docking scores, and hydrogen bond energy for the best score of each evaluated drug. The ligands order is according to descending best mean docking score

Order	Drug (Ligand)	Number of docked poses (n)	Mean±S.D	Minimum (The best score)	Maximum (The weakest score)	Minimum Hydrogen bonds Energy
1	Leucinamide	13	-149.34±24.69	-191.62	-96.92	-10.806700
2	Diovan	12	-117.37±11.51	-135.80	-97.35	-3.941330
3	Citalopram	15	-100.95±10.83	-111.38	-67.31	-2.500000
4	Amlodipine	13	-95.58±5.92	-108.14	-86.51	-8.001230
5	Donepezil	25	-88.25±12.08	-98.87	-41.22	-6.740170
6	Clonazepam	28	-86.62±15.68	-106.92	-54.83	-8.105320
7	Aspirin	15	-64.30±7.11	-73.09	-51.06	-5.580810
8	Depakin	16	-64.06±7.69	-74.21	-44.85	-3.490140
9	Memantine	29	-52.71±11.71	-75.29	-27.17	-4.214670
--	**Total**	166	-85.88±29.33	-191.62	-27.17	---

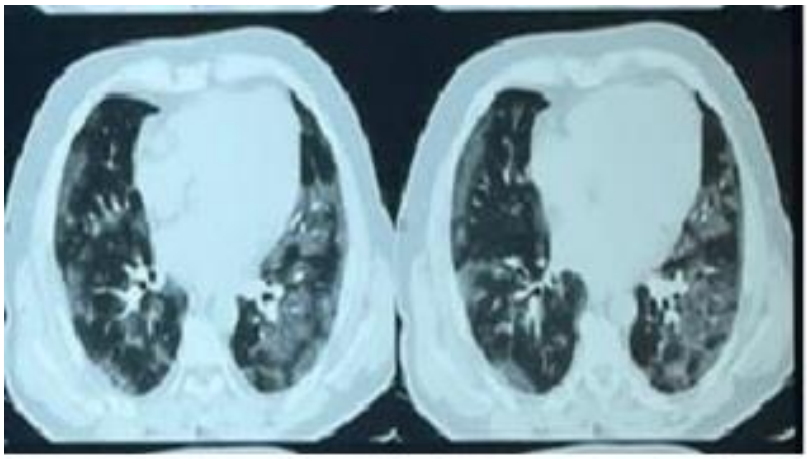


Figure 1: Chest computed tomography scan of the patient on admission to the ICU

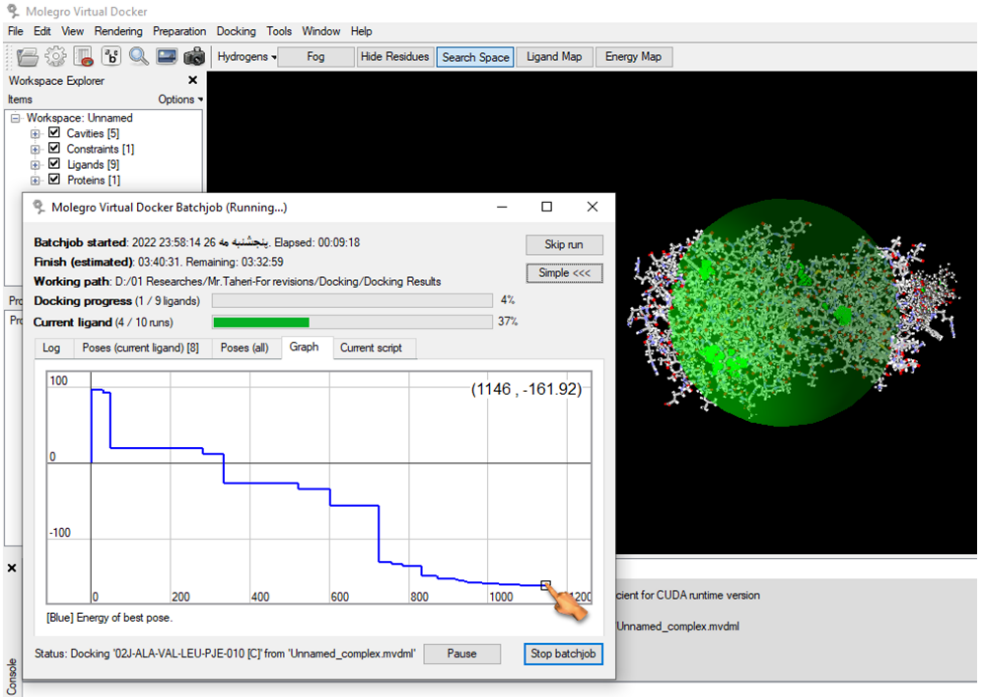


Figure 2: A view of Molegro virtual Docker software showing COVID-19 main protease and nine ligands during the calculation of interaction energy values and determination of DOS

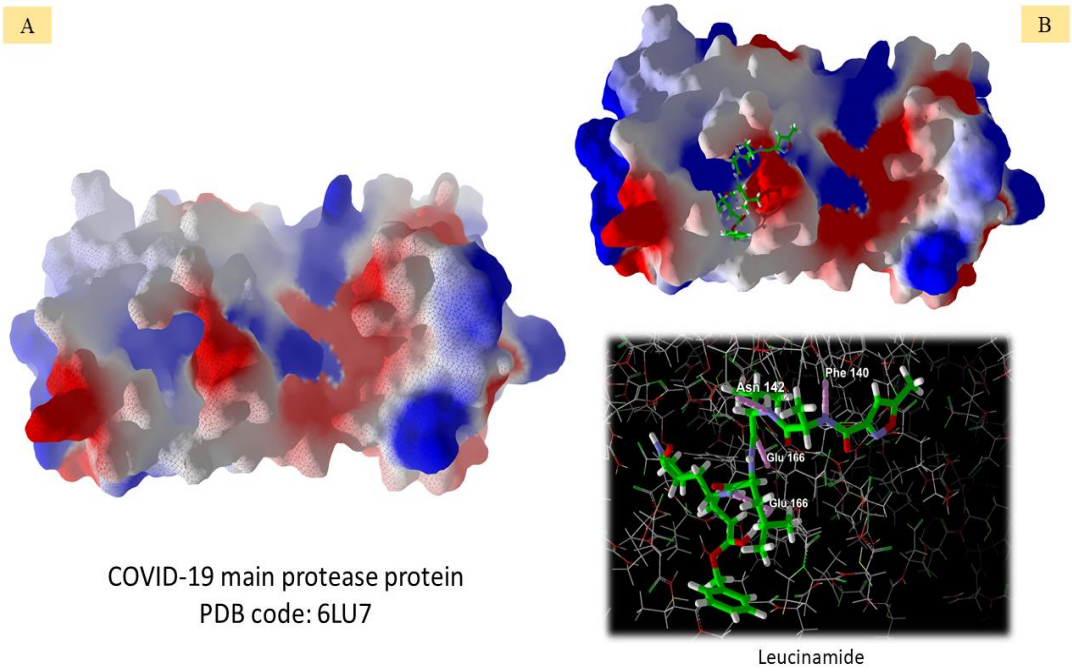


Figure 3: The 3D structure of COVID-19 main protease (A) shows the binding pocket and attachment pose of the Leucinamide molecule. Virtually, Leucinamide interacts with COVID-19 main protease at the best position with the highest DOS= -191.62. At this site, Leucinamide forms four hydrogen bonds with Asp 142; Phe 140; Glu 166 (bifurcated) (B)

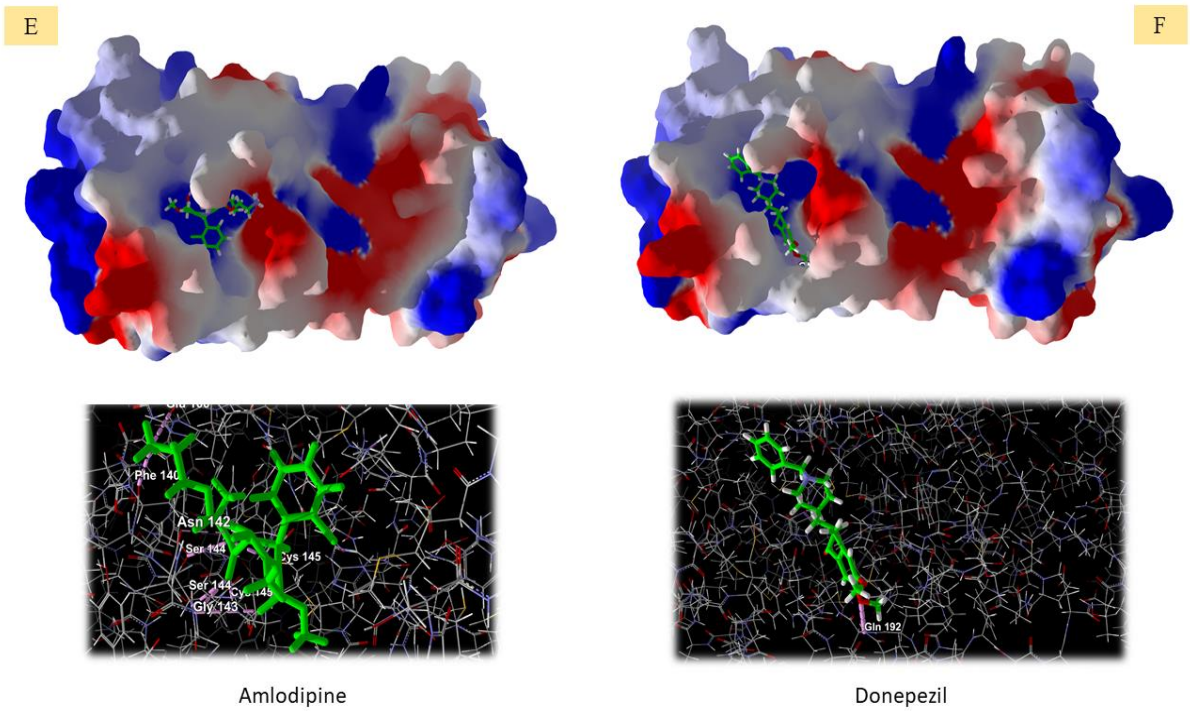


Figure 4: Virtually, COVID-19 main protease interacts with Diovan at the best position with DOS= -135.80. In this position, Diovan forms three hydrogen bonds with His 164 and His 41 (bifurcated) (C). Citalopram interacts with COVID-19 main protease and makes a hydrogen bond via Tyr 54, and the best DOS= -111.38 (D).

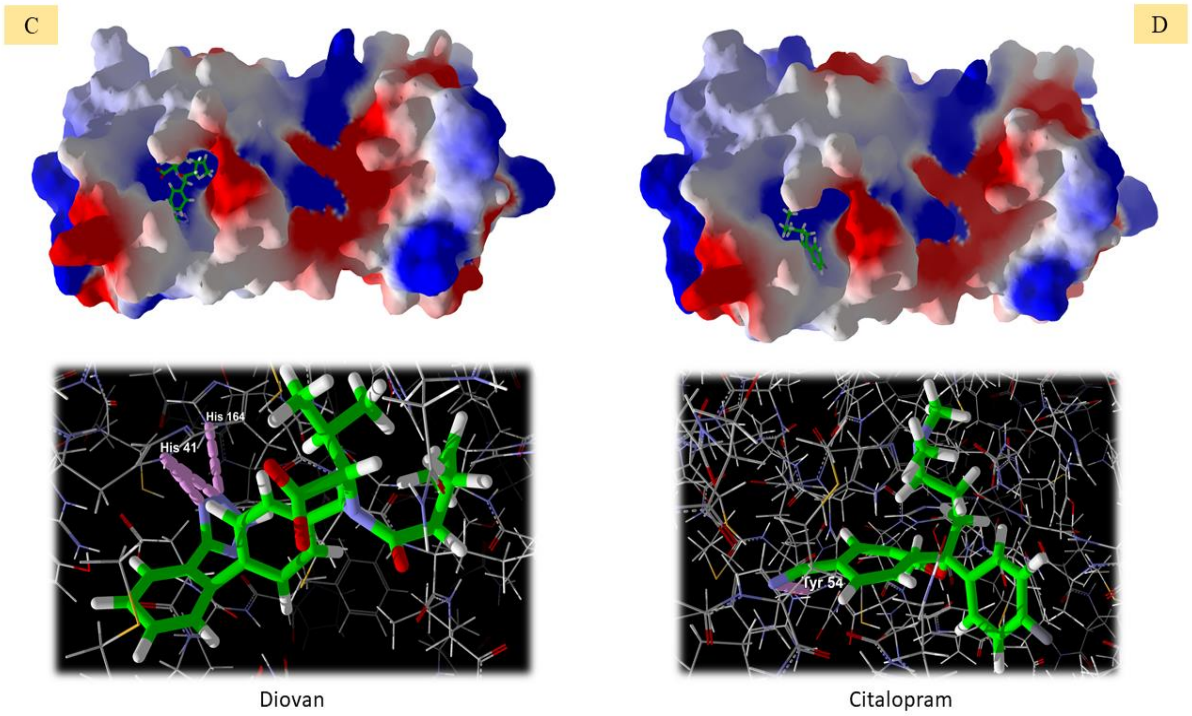


Figure 5: Virtually, Amlodipine interacts with COVID-19 main protease with DOS= -108.14. At this site, Amlodipine forms ten hydrogen bonds with Glu 166, and Phe 140, Asn 142, Gly 143 (bifurcated), Ser 144 (bifurcated), Cys 145 (trifurcated) (E). Donepezil interacts with COVID-19 main protease to form one hydrogen bond via Gln 192, with DOS= -98.87 (F).

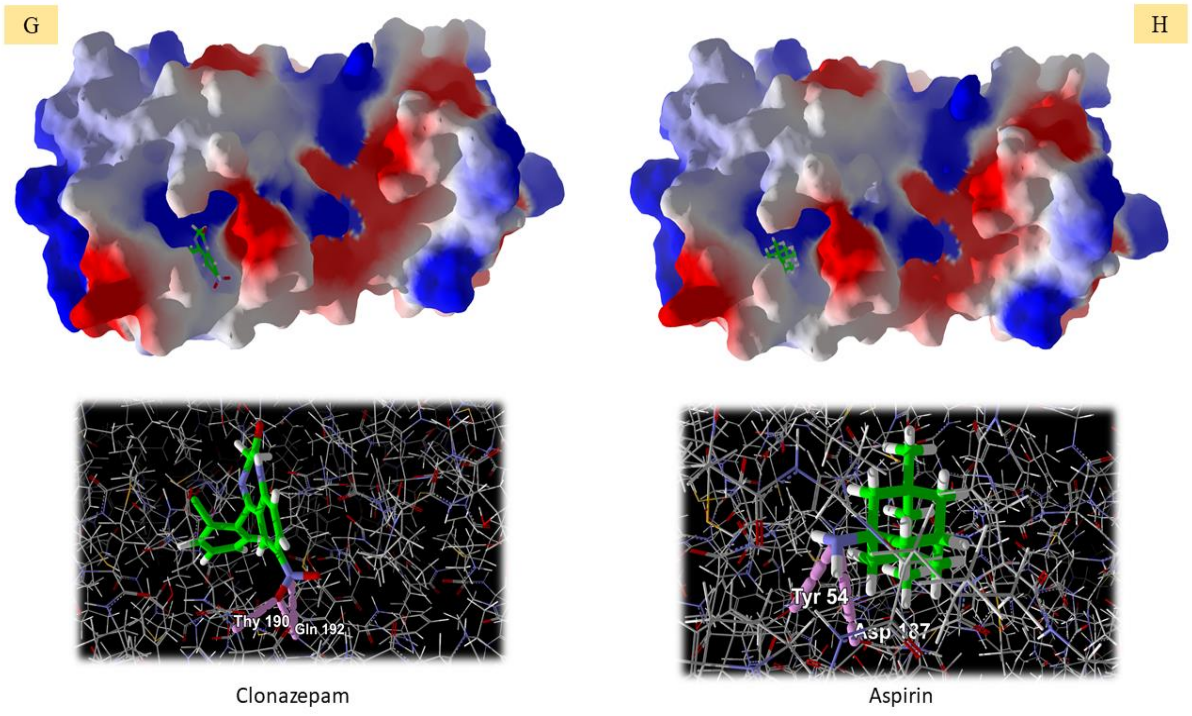


Figure 6: Virtually, Clonazepam interacts with COVID-19 main protease with DOS= -106.92. In this position, Clonazepam forms three hydrogen bonds with Gln 192 (bifurcated) and Tyr 190 (G). Aspirin interacts with COVID-19 main protease to form two hydrogen bonds via Tyr 54 and Asp 187, with DOS= -73.09 (H).

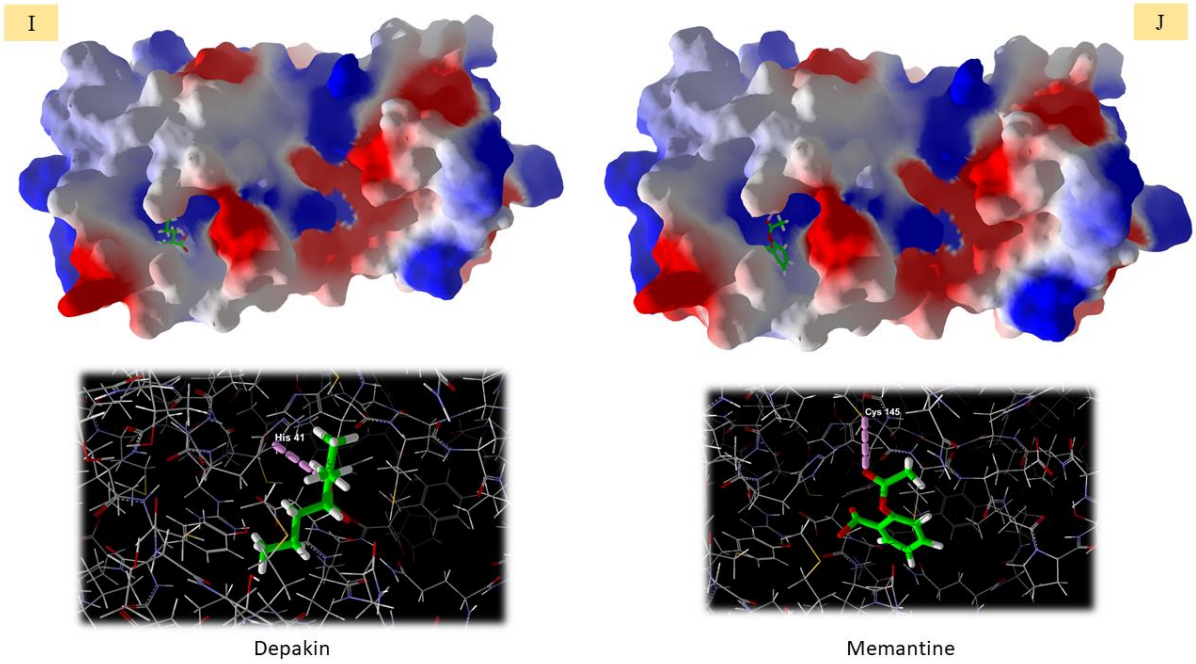


Figure 7: Virtually, Depakin interacts with COVID-19 main protease with DOS= -74.21. In this position, Depakin forms one hydrogen bond with His 41 (I). Memantine interacts with COVID-19 main protease to form one hydrogen bond via Cys 145 with DOS= -75.29 (J)

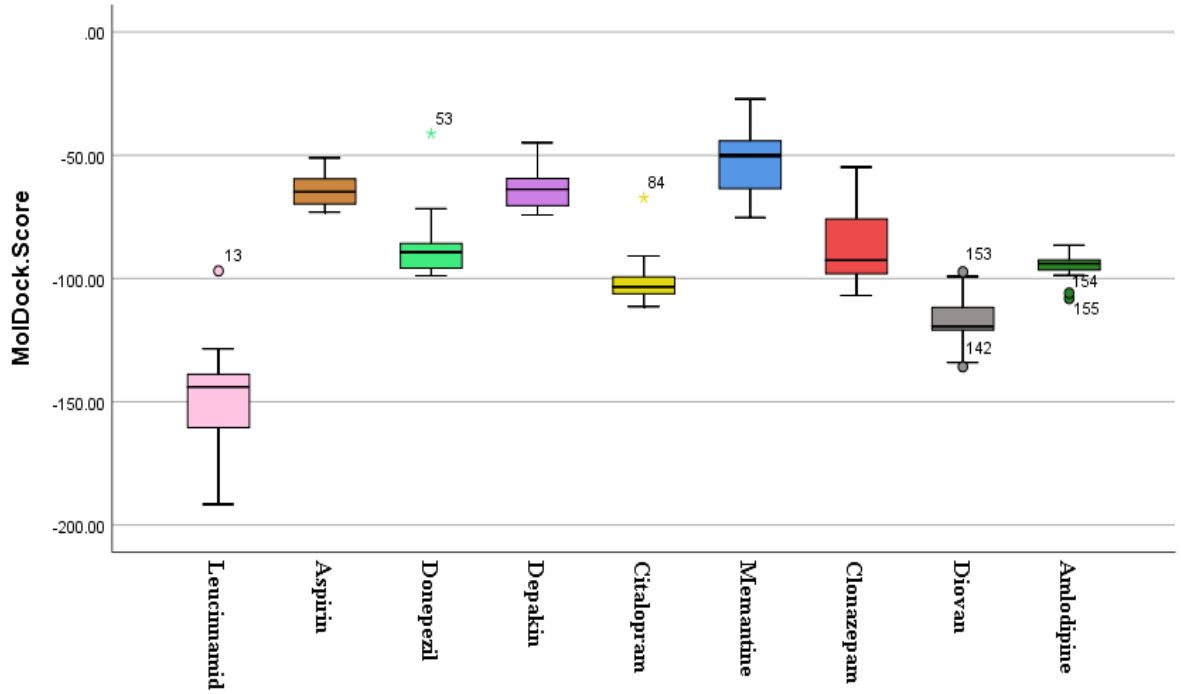


Figure 8: Comparative box-plot for Mean±SD of MolDock Scores of 9 ligand-protein interactions. Leucinamide plus eight administered drugs for the patient with Alzheimer's disease. We make a docking search between these nine compounds to elucidate the expected interaction between Alzheimer's disease drugs and COVID-19 main proteinase. Considering mean±sd of DOS values, Leucinamide showed the best score for others, followed by Diovan, Citalopram, Amlodipine, Donepezil, Clonazepam, Aspirin, Depakin, and Memantine, respectively.

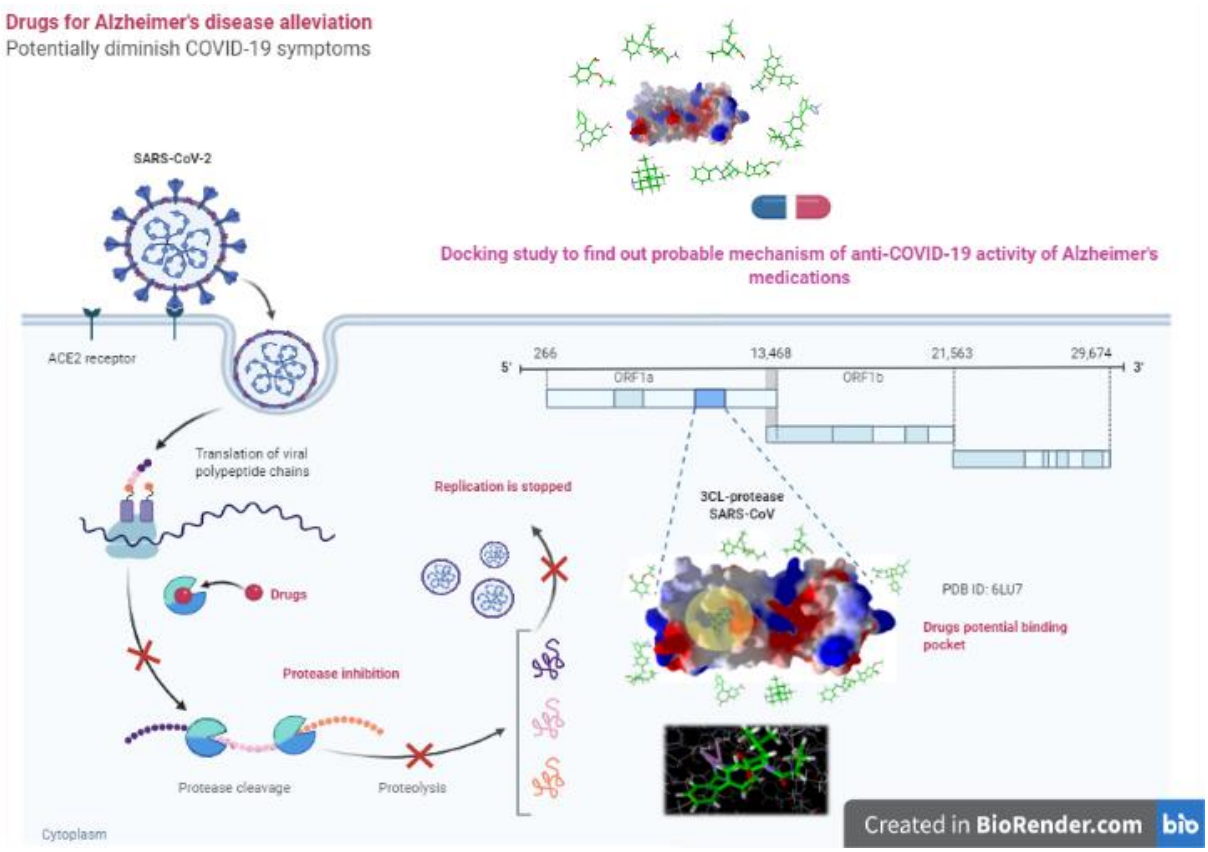


Figure 9: A graphical abstract depicting the probable mechanism of action of drugs used to alleviate Alzheimer's disease symptoms but interact with 3CL pro (COVID-19 main protease). It is expected that via such interactions, administered drugs for our case (an Alzheimer disease women) inactivate the 3CL pro, and virus replication dwindled. Note: this image is created in BioRender online software