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Purposeful scientific research is a basic pillar for the advancement of Iraq

Design of some compounds *in silico* as proposed materials to inhibit the angiotensin-converting enzyme-2 receptor for covid19

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ABSTRACT

The current study used the bioinformatics program to screen the bioactive compounds and antioxidant chemicals as potent compounds that inhibit the ACE-2 receptor (PDB ID: 1R42). Molecular docking was performed to dock many representative compounds of the active site in the target receptor protein within the chain (A) using version 0.8 of the virtual screen tool 'PyRx' and then the analysis was done using the 'discovery studio visualize' program. According to the highest affinity of binding, more than fifteen compounds were listed as leading molecules by using molecular docking tools. chloroquine phosphate was used as a control compound with a docking score (-6 kcal/mol) Among testing compounds, vitamin E derivatives such as tetramethyl-2-[(3E,7E) -4, 8, 12 – trimethyltrideca - 3, 7, 11-trienyl] -3, 4-dihydrochromen-6-ol and tocopherol were has the highest binding affinity − 8.1 kcal/ mol with stable interactions to the amino acid residues which present on the active site onto ACE-2 receptor. Ascorbic acid, palmitic acid and rutin had a good binding efficiency. The study proposes these compounds as potential inhibitors for target-specific ACE2 enzyme.

Keywords: ***In silico***, COVID -19 ACE2 Receptor, Vitamin E

1. Introduction

SARS –CoV -2 belongs to RNA viruses group, which are a large family of viruses causing serious diseases that range from the common-cold (like seasonal occurred viruses) to harder conditions like SARS-CoV and Mers- CoV (Abdelli *et al.*, 2021). Coronavirus has common proteins like envelope, nucleocapsid and spikes (Jafari and Ganjalikhany, 2021a). The protein of the spike of the virus SARS-CoV that binds to the surface receptors on human cells is critical to cause infection (Abubakar *et al.*, 2021). The single strand of RNA virus enhance identical receptor for SARS- CoV, i.e., angiotensin - converting enzyme -2 (ACE- 2) for infecting host cells, so it is needed for developing more effective drugs against that disease (Upreti *et al.*, 2021a). The progressed compelling medicines will not take a shorter time to perform during this pandemic issue (Madden *et al.*, 2020). The coronaviruses have specific sites of binding for ACE2 which serves as the entry points to mammalian cells (South, Brady and Flynn, 2020).

Mutations occurred in the domain of receptor-binding in the glycoprotein of spikes that play a very critical role in increasing the affinity of coronavirus to ACE-2 (Huentelman *et al.*, 2004). The ACE2 receptor affinity to SARS-CoV- 2 is higher than the traditional type of virus according to the high energy of the glycoprotein component of spikes (Ivanov *et al.*, 2021). Angiotensin-converting enzyme-2 (ACE-2) is proven to be critical for impacting both the immune systems and cardiovascular systems through two main important physiological mechanisms (Jafari and Ganjalikhany, 2021b). The human ACE-2 structure is recently described by x-ray crystallography in two forms: inhibitor bound and apo-bound. ACE-2 molecules are present mainly on the blood vessels surface, besides the epithelium of the lung and the intestine which are imperative to control immune reactions and the flow of the blood (Huentelman *et al.*, 2004). A comparison among these numerous structures expresses striking conformational changes in the active sites which impact many surrounding residues, including the ACE-2 residues, implicated in binding to the SARS-CoV protein of the spikes (Upreti *et al.*, 2021a). Researchers suggested that receptor is a potential main target of therapies and vaccines (Madden *et al.*, 2020). The inhibitors which block that receptor may make this harder for entrance of corona virus into host cells, which might significantly make the spreading of the virus slower then disappearing (South, Brady and Flynn, 2020). By bioinformatics, *in silico* ACE-2 inhibition by some molecules that obtained from certain essential antioxidant compounds of a nutrients and vitamins derivatives such as Tocopherol, which is a compound found mainly in Sunflower Seeds — 66%

DV per serving. 1 ounce: 10 mg. Almonds — 48% DV per serving. And Hazelnuts — 28% DV per serving. In silico approachs included using databases such as PubChem ,Protein bank database PBD and National centre for Biotechnology Information (NCBI) ,Also software such as chimera ,pyrix,and Discovery Studio 2021 Client which used for visualization and docking(Upreti *et al.*, 2021b) .The aim of this study is to use *In silico* approach to inhibit ACE-2 receptor with ligands chosen from antioxidant compounds as a means to prevent attack spike of covid -19 virus which represents as ligand to the ACE-2 receptor.

2-Material and methods

2.1. Protein and ligands preparation:

The enzyme ACE-2, which forms the main target in the virus of humans is obtained from a database of PDB (URL: https ://www.rcsb.org) which has the PDB ID: 1R42; besides selecting the protein in molecular docking which is based on the X- ray imagination. Proteins are been in PDB formats. The 1R42 angiotensin-converting enzyme - 2 (ACE -2) structure by X-ray crystallographic was prepared for docking study for all heteroatoms (ion, water, etc.) that were removed except chain-A of this structure via the use of chimera tool with Discovery Studio 2021 Client software. The binding site of protein to the A-chain was selected but other sites were removed.

2.1.1 Ligands Preparation:

Pubchem website https ://pubch em.ncbi.nlm.nih.gov used for obtaining phytochemicals 2-D structures represented as SDF format, furthermore by the option 'Open Babel' (software), these compounds were converted into PDB format. The reference molecule which used in molecular docking analysis is chloroquine phosphate (brand name Resochin) with Pubchem ID of CID-64927. Chloroquine phosphate (a commercial drug) is used as control drug in current study as a famous inhibitor of ACE-2.

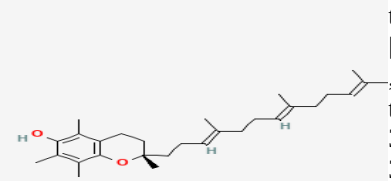
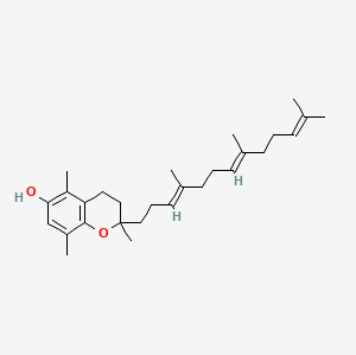
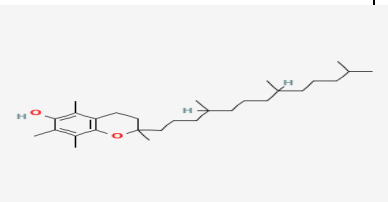
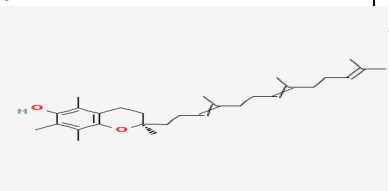
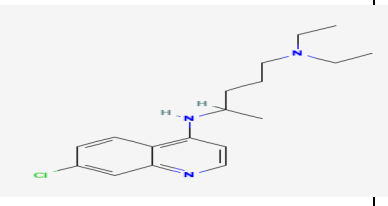
2.2 Molecular docking:

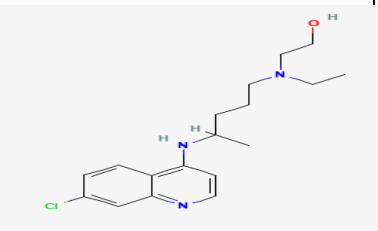
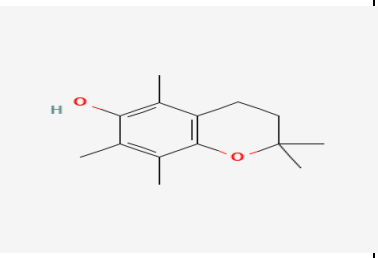
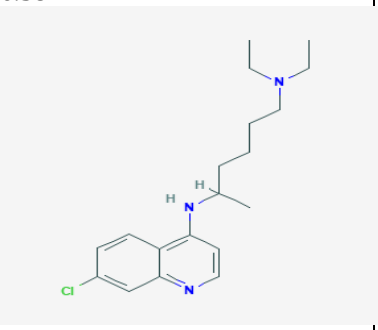
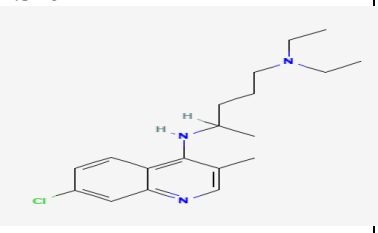
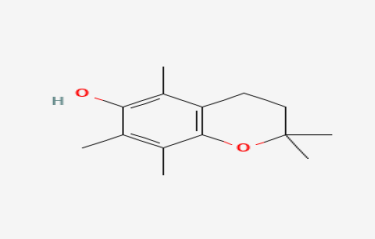
The *in-silico* study for ligands and receptors in docking analysis is performed for testing complexes of 1R42 structure (protein target) with antioxidant compounds as ligands to examine structural changes in conformation in this protein target in a specific way. In the current study, the virtual screening PyRx tool used the Vina option with Auto Dock 4.2 program and the Lamarckian algorithm to confirm the scoring function and to contribute much docking accuracy (Upreti *et al.*, 2021a). The protein target is composed of a total number of atoms 5218; 655 residues and five chains. The macromolecule has a chemical structure obtained by X-ray crystallography and a 3.00 Å resolution. The study continues the preparation of each target via eliminating all bounded ligands and the molecules of water through the Chimera tool 'UCSF'. Besides, all the chains were removed except chain-A, because it shows the single chain of ligand site of binding. Then, it was introduced to the PyRx program as a macromolecule. In this workflow, ligand molecules and protein were converted to related readable and suitable pdbqt file format by autodock option. All the studies of docking were applied as in a grid box and the possible ligand–receptor complex was documented. The dimensions are X = 75.862, Y = 65.436, and Z = 65.595 for docking the ligands which were 8 maximum suggestions and they were calculated for all ligands. Other software parameters were saved and each bond contained in the ligand was permitted to rotate, and the receptor was considered rigid. The final visualization of docked structures was applied by using the 3.0 Discovery Studio Visualizer program. Before the potentiality of compounds was tested against 1R42, a commercial ACE-2 inhibitor 'chloroquine phosphate' had been docked against 1R4L in order to give a comparative study (Upreti *et al.*, 2021a) .

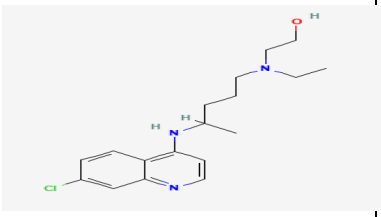
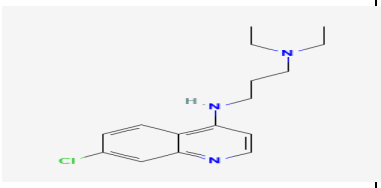
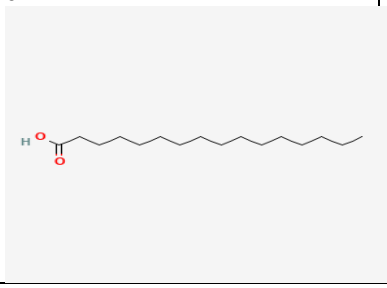
3- Results and discussion

The protein of spikes that binds to the membrane receptor onto host cells, angiotensin -converting enzyme-2 (ACE-2, EC 3.4.17.23) mediates viral fusion to the cell membrane (Abubakar *et al.*, 2021) Molecular docking was carried out for receptor proteins (ACE-2) to related antioxidant compounds as inhibitors such as derivatives of vitamin E and A, and ascorbic acid depending on the fact that less score of binding energy means higher docking scores (Pantsar and Poso, 2018) docking of inhibition ACE-2 enzyme has been done, a group of antioxidant compounds of derivatives vitamins such as vitamin E and A and C was an experiment in this study . The results showed that vitamin E derivatives were more affinity to interaction with chain A of the ACE2 enzyme which agrees with (Ahmad *et al.*, 2021) who mention that antioxidant compounds may support immunity against covid -19 infection, as shown in table (1). Chemical compounds which used as ligands with a binding affinity of the ligands with the receptor, when energy low affinity between ligand and receptor increases (Jafary, Jafari and Ganjalikhany, 2021a) .The RMSD values give the average deviation of the corresponding atoms of two proteins that are used to validate docking studies (Bell and Zhang, 2019). RMSD upper bounds match each atom of one conformation beside it in the other conformation was applied with ignoring of any symmetry. RMSD lower bounds that match atoms of each conformation besides the closest atom in the same type of element in the other conformation were also considered (Bell and Zhang, 2019)

Table 1: Ligands diagnosis with ACE2 molecules chain A as inhibitors

Ligand docking term	Binding Affinity kcal/mol	RMSD/ UB	RMSD/LB	Chemical name
1r42_11464420_uff_E =349.22	-8.1	2.383	6.473 	(2S) -2, 5, 7 ,8-tetramethyl -2-[(3E,7E)- 4 , 8 ,12-trimethyltrideca-3, 7, 11- trienyl]-3, 4-dihydrochromen-6 - ol
1r42_9844470_uff_E= 323.05	-7.9	0	0 	Epsilon-Tokoferol; Beta-Tocotienol; E-Tocopherol; (-)-Beta-Tocotrienol
1r42_14985_uff_E=28 8.57	-7.7	0	0 	VITAMIN E; Alpha-Tocopherol; 59-02-9; D-Alpha-Tocopherol; 5,7,8-Trimethyltocol; (+)-Alpha-Tocopherol; Alpha-Vitamin E; Aquasol E; ...
1r42_2116_uff_E=295 .43	-7.3	0	0 	-alpha-tocopherol
1r42_644087_uff_E=3 40.40	-7.3	0	0 	1721-51-3; AKOS030228538
1r42_2719_uff_E=262 .55	-6.4	0	0 	Chloroquine; 54-05-7; Aralen; Chlorochin; Chloraquine; Artrichin; Chloroquinium; Chloroquina; ...

1r42_3652_uff_E=280.62	-6.4	0	0 	Hydroxychloroquine; 118-42-3; Plaquenil; Oxichloroquine; Hidroxicloroquina; Hydroxychloroquinum; Oxichlorochine; WIN 1258; ...
1r42_99479_uff_E=192.86	-6.3	0	0 	2,2,5,7,8-Pentamethyl-6-Chromanol; Chromanol; 950-99-2; Chromane C1; Chroman C1; 2,2,5,7,8-Pentamethylchroman-6-Ol; PMHCR; APC-100; ..
1r42_224725_uff_E=290.52	-6.1	8.883	6.382 	CHEMBL423184; NSC13447; SCHEMBL17640854; BDBM50408768; NSC-13447; DS-011644; N-(7-Chloroquinolin-4-Yl)- N , N-Diethyl-Hexane-1,5-Diamine; N-[5-(Diethylamino) -1-Methylpentyl]-7-Chloroquinoline-4- Amine; ...
1r42_66553_uff_E=362.18	-6	4.413	2.946 	Sontoquine; Sontochin; 3-Methylchloroquine; CHEMBL343728; 85-10-9; Nivaquine C; UNII-U34E688BAM; NSC2088
1r42_99479_uff_E=192.86	-6	3.315	1.48 	2,2,5,7,8-Pentamethyl-6-Chromanol; Chromanol; 950-99-2; Chromane C1; Chroman C1; 2,2,5,7,8-Pentamethylchroman-6-Ol; PMHCR; APC-100; ...

1r42_3652_uff_E=280.62	-5.9	22.142	19.778 	Hydroxychloroquine; 118-42-3; Plaquenil; Oxichloroquine; Hidroxicloroquina; Hydroxychloroquinum; Oxichlorochine; WIN 1258; ...
1r42_3805581_uff_E=239.08	-5.7	7.766	6.043 	AQ-13 Free Base; AQ-13; UNII-4K7VT5621X; Ro 47-0543; 4K7VT5621X; 32571-49-6; SN 9854; CHEMBL1440337; ...
1r42_985_uff_E=57.46	-5.5	0	0 	Palmitic Acid; Hexadecanoic Acid; 57-10-3; Cetylic Acid; Palmitate; N-Hexadecanoic Acid; Hexadecylic Acid; Hydrofol;

3.1Chloroquine phosphate as Control Ligand

The reference molecule that was used for the entire molecular docking is chloroquine phosphate (brand name is Resochin) with Pubchem ID of CID - 64927 which was obtained from the PubChem website. The Chloroquine phosphate (commercial drug) that used as the control drug in the current study is a famous inhibitor for ACE-2 as shown in figure (1) interaction status of experiment control ligand.

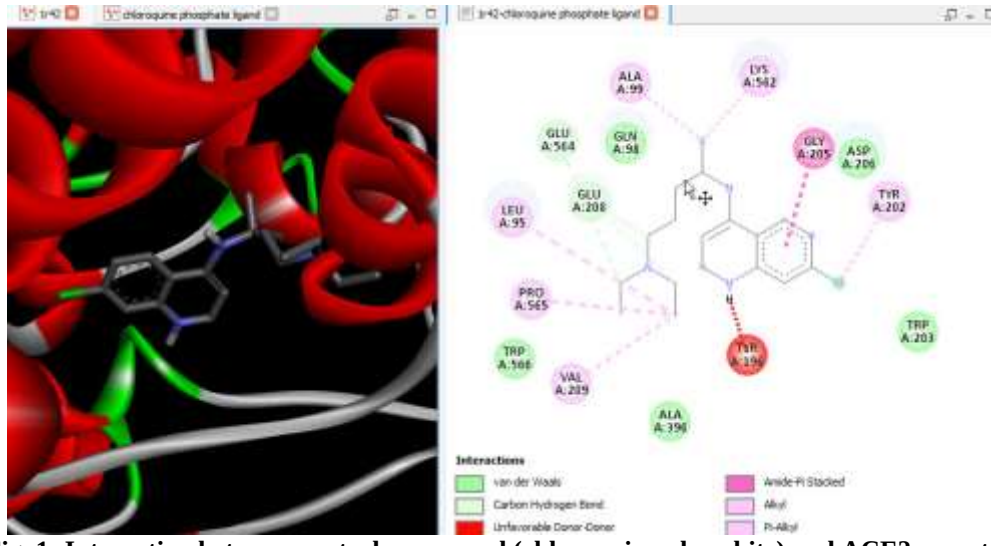


Fig. 1: Interaction between control compound (chloroquine phosphite) and ACE2 receptor

Table 2: Chloroquine phosphate ligand interaction with amino acids of ACE2 receptor location number within chain and type of bonds connection

Amino acid	Location within chaine	Bonds type
ALA	99	pi-Alkyle
LYS	562	pi-Alkyle
GLY	502	Amid pi stacked
TYR	202	Pi Alkyle
TYR	196	Unfavorable donor-donor
VAL	209	Alkyle
PRO	565	Alkyle
GLU	208	Carbone hydrogen bond
GLU	564	Carbone hydrogen bond
GLU	98	Van der waals
ASP	206	Van der waals

As shown in figure (2) the receptor pocket and docking environment included charging, ionizing, hydrophobicity and SAS were suitable to interact ligand within receptor pocket. Chloroquine phosphate used as antimalarial drugs hydroxychloroquine and chloroquine (Upreti *et al.*, 2021b) in the early spread of covid 19 infection was recommended for treating SARS-CoV-2 disease and it has various side effects, so, natural compounds better to be used. Natural compounds may boost immunity besides curing a wide range of disease (Zhan *et al*., 2020).

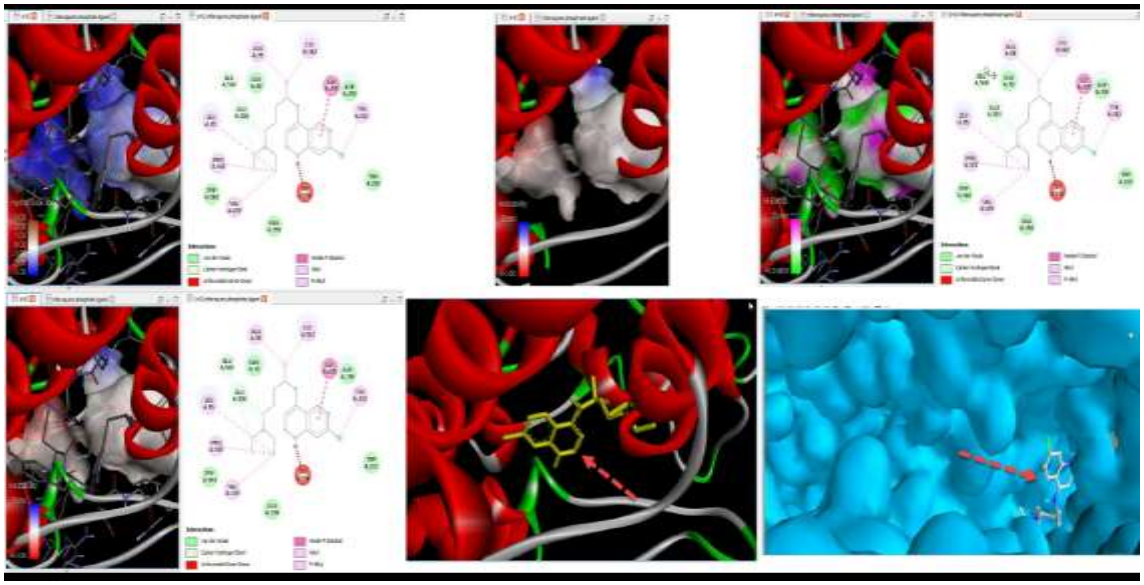


Fig. 2: Three dimensions images between chloroquine phosphate ligand and ACE2 chain A

3.2 Antioxidant of vitamin A derivatives compound ligand

3.2.1Tetramethyl-2- [(3 E, 7E)-4, 8, 12-trimethyltrideca- 3, 7, 11-trienyl] -3, 4-dihydrochromen- 6- ol

ACE-2 is the best target to inhibit the 2019- CoV, because of its higher affinity for spike glycoprotein of SARS-Cov2. Spike glycoprotein has the most potent role in the ttachment of viruses, invasion and entry to the mammalian cell. In the current study, the best inhibitor to ACE-2 enzyme was (2S) - 2 , 5 , 7 , 8 - tetramethyl-2 - [(3E,7E) -4, 8, 12 – trimethyltrideca - 3, 7, 11- trienyl]-3, 4-dihydrochromen -6- ol that is one of vitamin E derivatives (Jin *et al*., 2021). As shown in table (3) the ligand interaction with chain A of ACE-2 receptor with twelve amino acids, also two types of bonds constructed between ligand and receptor van der Waals and alkyl bonds. The binding energy was low -8.1 which increases the affinity between the two compounds. Basically, the RMSD values were used to validate molecular docking studies (Upreti *et al.*, 2021a). The RMSD values between experimental ligand with docked ligand (2S) - 2, 5, 7, 8- tetramethyl-2-[(3E,7E) -4,8,12-trimethyltrideca-3,7,11-trienyl] -3, 4-dihydrochromen-6 -ol) were 0.0 angstrom, which was perfectly acceptable. As shown in table (3) the interaction between amino acids and the type of the ligand represented the compound (2S)-2,5,7,8-tetramethyl-2- [(3E, 7E)-4,8,12-trimethyltrideca-3, 7, 11-trienyl] -3,4- dihydrochromen-6-ol and chain A of ACE-2 receptor. The virtual screening of antioxidant compound (n = 13) was applied by using the docking tools for active sites , and for the target protein the PyRx tool was used.

Table 3: Amino acids of ACE2 receptors interaction with tetramethyl - 2- [(3E, 7E)- 4, 8, 12 - trimethyltrideca- 3, 7, 11- trienyl] -3,4-dihydrochromen-6- ol ligand and bonds type

Amino acid	Location number within receptor	Bond type
PHE	32	Van-der Waals
ASP	350	Van-der Waals
TRE	349	Van-der Waals
SER	47	Van-der Waals
SER	44	Van-der Waals
SER	43	Van-der Waals
TYR	385	Van-der Waals
PHE	40	alkyl
LUE	73	alkyl
TRP	69	alkyl
LEU	391	alkyl
ARG	393	alkyl

The results of this study showed the best ligand interact with chain A of ACE2 receptor was (2S)-2, 5 ,7 ,8 - tetramethyl-2- [(3E,7E)-4,8,12-trimethyltrideca- 3,7,11-trienyl]-3, 4-dihydrochromen-6 - ol which is type of vitamin A derivative as shown in figure (3).

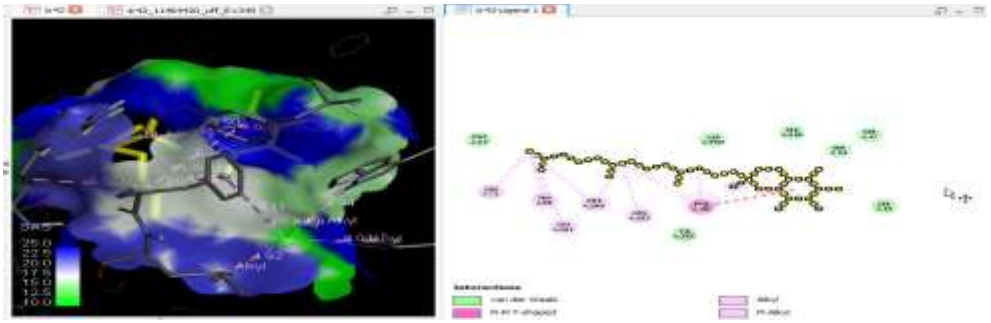


Fig. 3: Ligand interaction and bonds type between (2S)-2,5,7,8-tetramethyl-2-[(3E,7E)-4,8,12-trimethyltrideca-3,7,11-trienyl]-3,4-dihydrochromen-6-ol and chain-A of ACE2 receptor.

Define ligand by discovery studio visualizer software permits study to detect docking environment included hydrophobicity, charging, ionizing and SAS (Pantsar and Poso, 2018) as shown in figure (4). The hydrophobicity of nonpolar groups within receptor amino acids pushes towards ligand binding, also Ionization of changing positive and negative charge increased affinity between two molecules (Upreti *et al.*, 2021a)

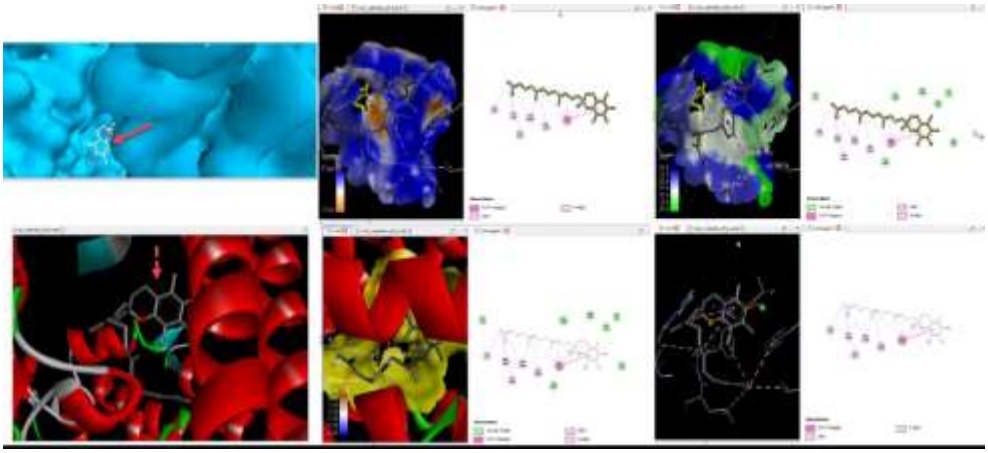


Fig. 4: Docking of (2S) -2,5,7,8-tetramethyl-2- [(3E,7E)-4,8,12-trimethyltrideca-3 ,7, 11-trienyl]- 3, 4- as a ligand with ACE2 enzyme showed high affinity with dock score -8.1 which consider best inhibitor

3.2.2 Epsilon- Tocopherol

Tocopherol was the second compound gets high score of binding -7. 9 according to table (4), so the affinity between ligand and ACE2 enzyme. As shown in table (4) amino acids location and types of bonds reflect the higher interaction between receptor and ligand.

Table 4: The amino acids interact with tocopherol ligand, their location within chain A of ACE2 receptor and bonds

Amino acid	location	Bonds type
TRP	349	Alkyl
PHE	390	Alkyl-pi
LEU	391	Alkyl-pi
ARG	393	Alkyl-pi
PHE	40	Alkyl-pi

Ionization between ligand (tochopherol) and receptor ACE2 showed clearly in figure(5) more than two amino acids shared between acid and base environment . Ionization is defined as the process in which the atom or a molecule has a negative or positive charge via gaining or losing electrons, in conjunction with other chemical changes. Resulted in electrical charged atom or molecule then is called an ion (Wilschefski and Baxter, 2019).

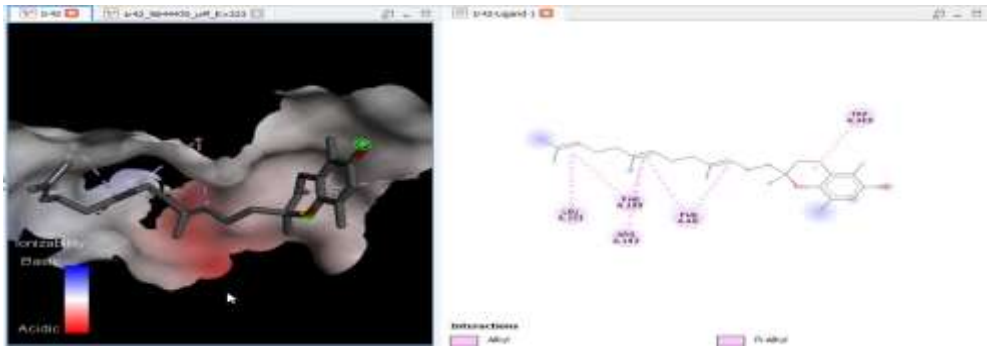


Fig 5: interaction view between amino acids of ACE2 receptor and tocopherol ligand ,pocket receptor appeared clearly with Discovery Studio 2021 Client software

3.3 Ascorbic acid

Ascorbic acid was uses as a ligand to ACE2 receptor the anergy required for binding was -5.5 kcal/mol which means its affinity is less than the control compound chloroquine phosphate -6 kcal/mol. That represents lower energy of binding score (higher scores of docking) (Teralı, Baddal and Gülcan, 2020) compared to the energy of binding of chloroquine phosphate (-6.8 kcal/ mol), the commercial and standard ACE-2 inhibitor. As shown in figure (6) the interaction between ligand and receptor was done by three amino acids which included (PHE 464,VAL463 and TRP 473) ,Also the bonds that connect ligand to amino acids of receptor were hydrogen bonds.

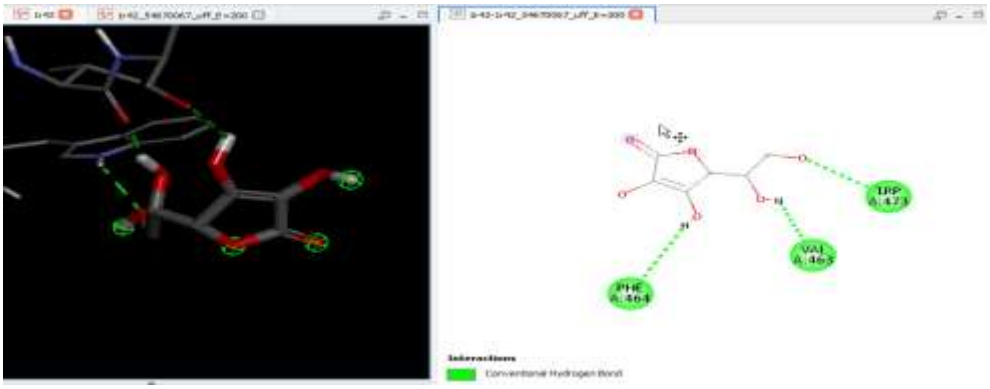


Fig. 6: Interaction between ascorbic acid as ligand and ACE2 receptor, three amino acids connect to chain a of ACE2 enzyme by hydrogen bonds

3.4 Palmitic Acid

Palmitic acid is a saturated fatty acid related to vitamin A metabolism (Yang *et al.*, 2021). The compound was used as a ligand for ACE2 receptor. The result showed less docking score in contrast with the control compound chloroquine phosphate of about -5.5 kcal/mol, therefore that reduce the affinity of used palmitic acid as ligand with ACE2 receptor. More than three amino acids interact with ligand compounds as shown in table (5).

Amino acid	Location number within receptor	Bonds type
SER	47	hydrogen bond
SER	43	hydrogen bond
SER	44	hydrogen bond
PHE	40	Alkyl bond
ARG	393	Alkyl bond
PHE	390	Alkyl bond
MET	62	Van-der Waals
TRP	349	Van-der Waals
ASP	350	Van-der Waals

Table 5: pocket receptor-ligand amino acids with location number and bonds type

Three types of bonds connected ligand compounds to amino acids within receptor pockets which included hydrogen bonds, van der Waals bonds and alkyl bonds as shown in figure (7).

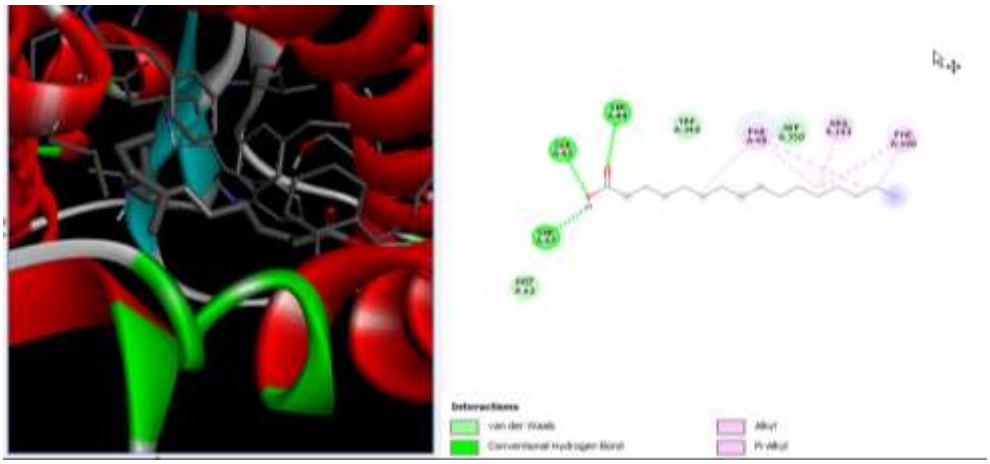


Fig. 7: Three-dimension image depicted interaction between palmitic acid (ligand) and receptor (ACE2), Amino acids and bonds form receptor pocket

As shown in figure (8) Hydrophobic interactions drive ligand-receptor recognition for activation and inhibition (Wright *et al.*, 2004) Hydrophobicity is defined as the association of nonpolar groups and molecules of aqueous environment that arises from the tendency of water and excludes nonpolar molecules (Möllers *et al.*, 2020). palmitic acid as saturated fatty acid had less affinity towards ACE-2 receptor in contrast with vitamin E derivatives. in spite of that docking score -5.5 kcal/mol consider good aas a ligand.

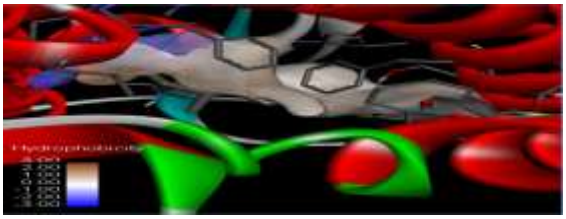


Fig. 8: hydrophobicity status of interaction between ligand palmitic acid and receptor ACE

4. Conclusion

The study results found that vitamin E derivatives such as 2S) -2, 5,7 , 8 -tetramethyl-2-[(3E,7E)- 4,8,12 -trimethyltrideca-3, 7, 11-trienyl] 3,4-dihydrochromen-6- ol and tocopherol had higher docking score of about -8.1 kcal/mol in contrast with standard control compound chloroquine phosphate -6 kcal/mo. These compounds are found in the proportion of 66% Sunflower Seeds, Almonds 48%, and Hazelnuts 28%. The other compound such as Ascorbic acid and palmitic acid had less affinity because docking score of about -5 kcal/mol in contrast with the reference compound chloroquine phosphate. The study proposes that the tested compounds are the potential to develop target specific inhibitors for ACE-2 enzyme.

5. Recommendation

This study urges and recommended to use of vitamin E and its derivatives continuously especially in such a period of covid 19 pandemic. These compounds consider competent inhibitors which reduced the binding covid-19 spikes to ACE2 receptor, subsequently supporting human immunity.

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