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THE MOLEULAR DOCKING STUDY OF SIDDHA DRUG PACHAI KARPOORA MATHIRAI TARGETING NOVEL CORONA VIRUS ANGIOTENSIN CONVERTING ENZYME(ACE 2) RECEPTOR

Dr.R.Saraswathi,
-Agasthiyar siddha clinic- Jeyang kondam,
Dr.A.Elavarasi
-Associate professor, Sir isac newton siddha medical college and hospital, Nagappatinam.

ABSTRACT

SARS –CoV is a pandemic virus that caused infection and death in many countries.The virus infect the human cells by binding via ACE-2 receptors through the spike protein of the virus with furins help causing membrane fusion leading to covid -19- cell entry.Our present work is based on molecular docking and dynamics simulation permed to spike protein –ACE-2 interface complex,ACE- 2 receptor[5][6]. Binding of phytocomponents of pachai karpoora mathiarai with the core amino acids (31 LYS and 353 LYS) of the target by forming hydrogen bond will hinder the function of the target Angiotensin-converting enzyme 2 (ACE2) receptors - PDB- 2AJF being recognized as binding site for novel corona virus for its pathogenesis essential for host-viral interaction. Thereby phytocomponents which inhibit the target ACE-2 may act as a potential therapeutic agent for management of COVID-19 and related symptoms. pachai karpoora mathiarai is traditional siddha drug used to treat the all type of fever in siddha system of medicine.

INTRODUCTION

Corona viruses are enveloped viruses with appositive sense ,single strand RNA genome.Corona virus spike protein has been reported as significant part of the virus host cell entry.SARS –Cov-2 bind to the human angiotensin converting enzyme-2(ACE_2)through the viral spike protein ,which triggers the entry of infectious SARS-CoV-2.ACE -2 is a cardio cerebral vascular protection factor found in many tissues, including kidney,Intestine,Lungs,skeletol muscles and Nervous system.Besides, it's played an important role in regulating blood pressure and arteriosclerosis mechanism as well as it consider a major binding target for SARS-CoV-2 spike protein of COVID -19 . Total of 10 bioactive lead compounds were retrieved from the herbs present in the formulations. From reported data of the herb, the lead molecules such as Vaccenic acid, Aloin-A and Aloe-emodin possess 100% binding efficacy by interacting with both the core target amino acids (31 LYS and 353 LYS) present on the target. Followed by this other phytocompounds such as Cinnamic acid, Grandisin, LicarinA, Elemicin and Gibberellic acid possess 50% affinity by binding with one of the target amino acid either with 31 LYS or with 353 LYS present on the target receptor ACE-2.[12]

KEY WORDS

Pachai karpoora mathirai, siddha medicine, Angiotensin converting enzyme -2,corona virus,phyto compounds.

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MATERIALS AND METHODS[13][14][11]

Name of the formulation: *Pacchai Karpoora Mathirai*

Ingridients of pachai karpoora mathirai

- **Cinnamomum Verum**
- **Myristica fragrans**
- **Croton tiglium**
- **Aloe vera**

List of Phytocomponents Selected for docking

S. N	Name of the Herb	Phyto components
1.	**Cinnamomum Verum**	• Cinnamaldehyd • Caryophyllene • Cinnamic acid[7]
2.	**Myristical fragrans**	• Grandisin • LicarinA • Elemicin[8]
3.	**Crotin tiglium**	• Vaccenic acid • Gibberellic acid[9]
4.	**Alovera**	• Aloin • Aloe-emodin[10]

Objective:[1][2][3][4]

Binding of phytocomponents with the core amino acids (31 LYS and 353 LYS) of the target by forming hydrogen bond will hinder the function of the target Angiotensin-converting enzyme 2 (ACE2) receptors - PDB- 2AJF being recognized as binding site for novel corona virus for its pathogenesis essential for host-viral interaction. Thereby phytocomponents which inhibit the target ACE-2 may act as a potential therapeutic agent for management of COVID-19 and related symptoms.

PDB	Name of the Target
2AJF	Angiotensin-converting enzyme 2 (ACE2) receptor

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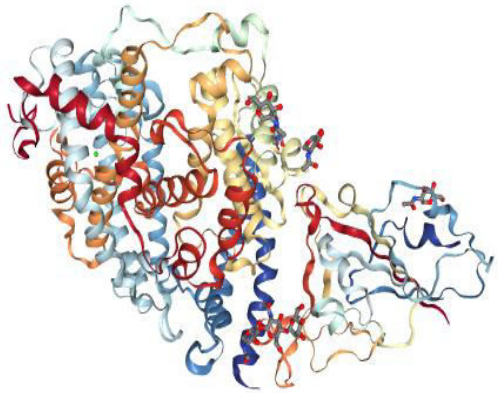
3D- Structure of Angiotensin-converting enzyme 2 (ACE2) receptor- PDB 2AJF



RECEPTOR STRUCTURE

TARGET SELECTION AND PREPARATION

Crystalline structure of the target protein Angiotensin-converting enzyme 2 (ACE2) receptor- PDB 2AJF was retrieved from protein data bank and protein clean-up process was done and essential missing hydrogen atom were being added. Different orientation of the lead molecules with respect to the target protein was evaluated by Autodock program and the best dock pose was selected based on the interaction study analysis.

Methodology

Docking calculations were carried out for retrieved phytocomponents against target protein ACE-2. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools (*Morris, Goodsell et al., 1998*). Affinity (grid) maps of ×× Å grid points and 0.375 Å spacing were generated using the Autogrid program (*Morris, Goodsell et al., 1998*). AutoDock parameter set- and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively. Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method (*Solis and Wets, 1981*). Initial position, orientation, and torsions of the ligand molecules were set randomly. All rotatable torsions were released during docking. Each docking experiment was derived from 2 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

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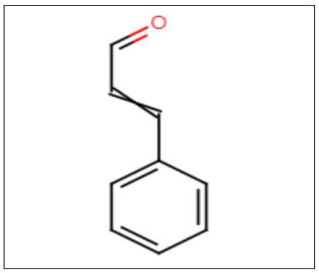
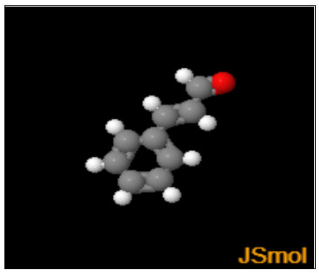
2D and 3D Structure of Selected Ligands

Cinnamaldehyde

Ligand in 2D

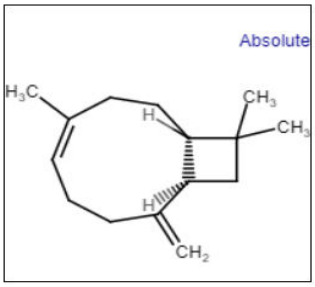


Ligand in 3D

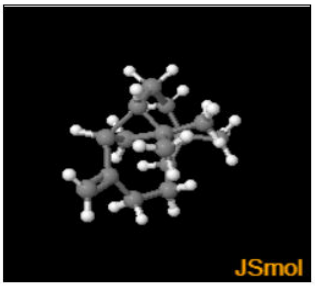


Caryophyllene

Ligand in 2D

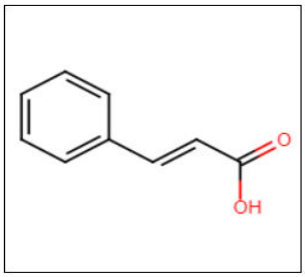


Ligand in 3D

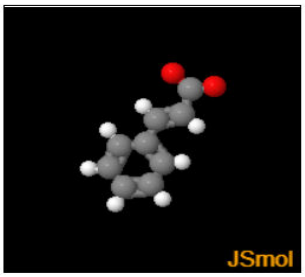


Cinnamic acid

Ligand in 2D



Ligand in 3D



Grandisin

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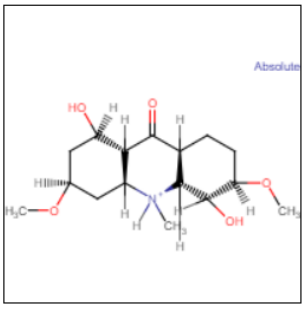
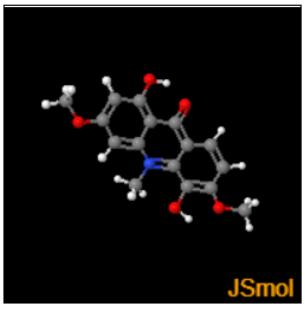
Ligand in 2D

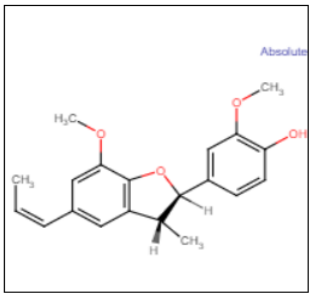


Ligand in 3D

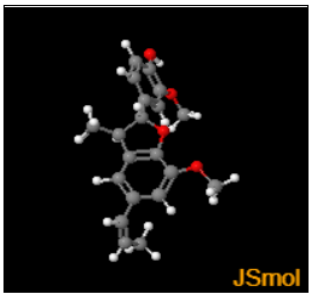


licarinA

Ligand in 2D

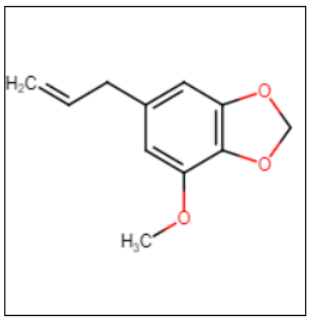


Ligand in 3D

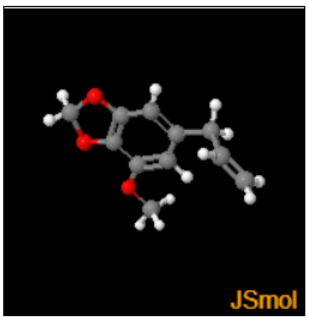


Elemicin

Ligand in 2D



Ligand in 3D



cis-Vaccenic acid

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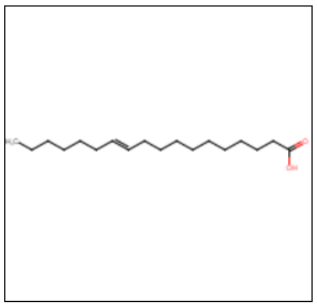
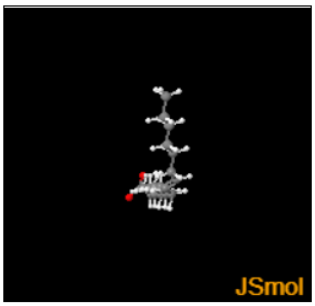
Ligand in 2D

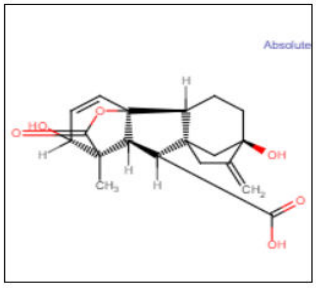


Ligand in 3D



Gibberellic acid

Ligand in 2D

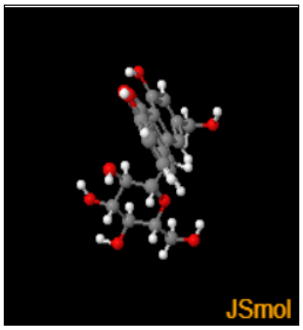


Ligand in 3D

Aloin-A

Ligand in 2D

Ligand in 3D



Aloe-emodin

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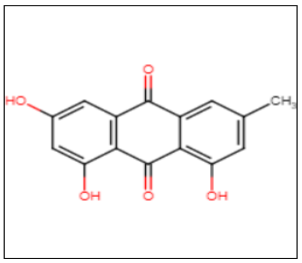
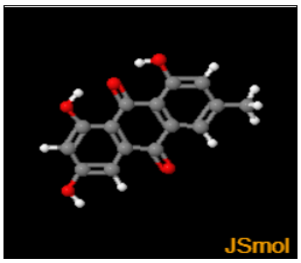


Ligand in 3D



Ligand Properties of the Compounds Selected for Docking Analysis

Compound	Molar weight g/mol	Molecular Formula	H Bond Donor	H Bond Acceptor	Rotatable bonds
Cinnamaldehyde	132.162 g/mol	C9H8O	0	1	2
Caryophyllene	204.35 g/mol	$C_{15}H_{24}$	0	0	0
Cinnamic acid	148.16 g/mol	$C_9H_8O_2$	1	2	2
Grandisin	276.37 g/mol	$C_{16}H_{24}N_2O_2$	1	4	0
licarinA	326.4 g/mol	$C_{20}H_{22}O_4$	1	4	4
Elemicin	208.25 g/mol	$C_{12}H_{16}O_3$	0	3	5
cis-Vaccenic acid	282.5 g/mol	$C_{18}H_{34}O_2$	1	2	15
Gibberellic acid	346.4 g/mol	$C_{19}H_{22}O_6$	3	6	1
Aloin-A	418.4 g/mol	$C_{21}H_{22}O_9$	7	9	3
Aloe-emodin	270.24 g/mol	$C_{15}H_{10}O_5$	3	5	1

Docking Pose

Cinnamaldehyde with Angiotensin-converting enzyme 2 (ACE2) receptor- PDB 2AJF

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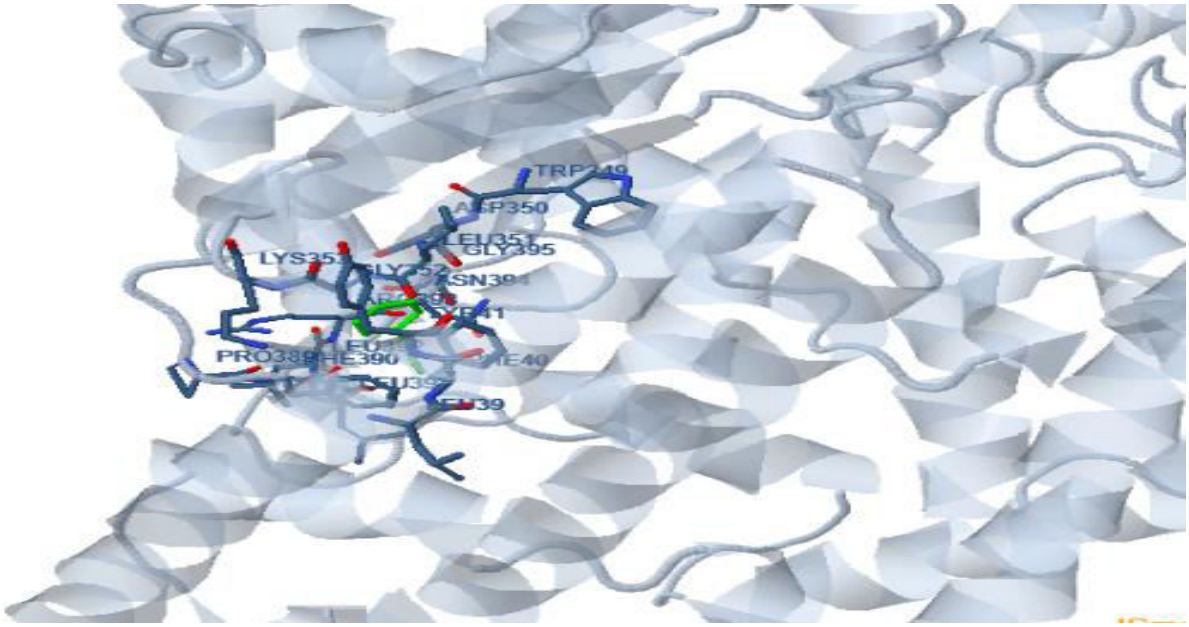
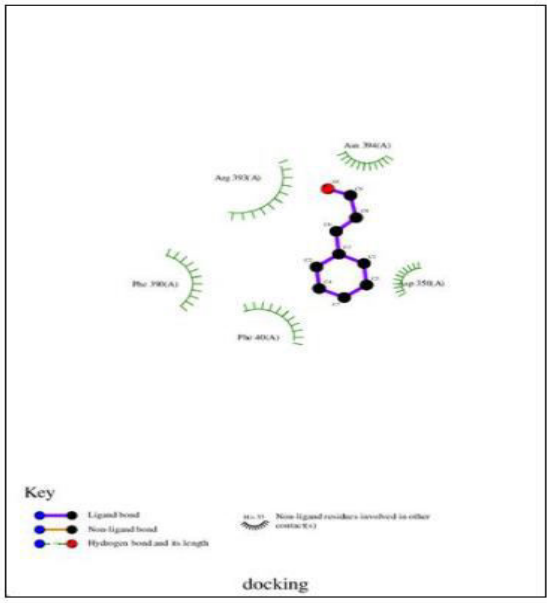


2D Interaction Plot Analysis



Hydrogen bond plotting with core amino acid Residues

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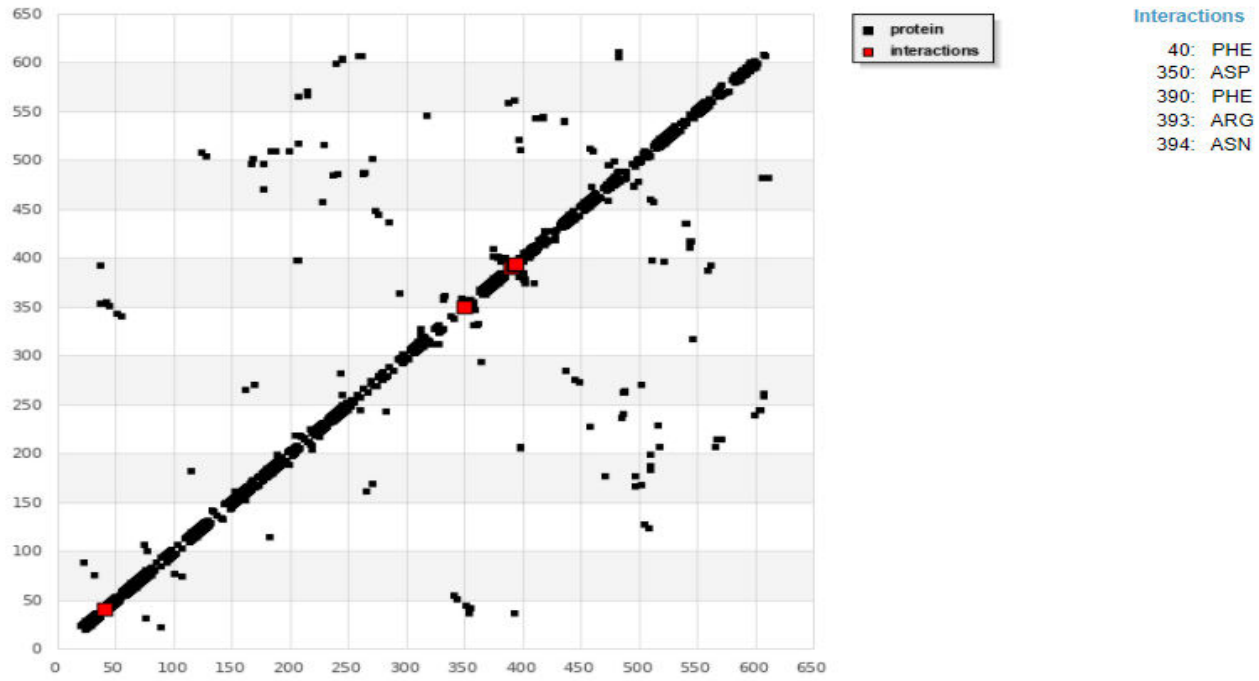
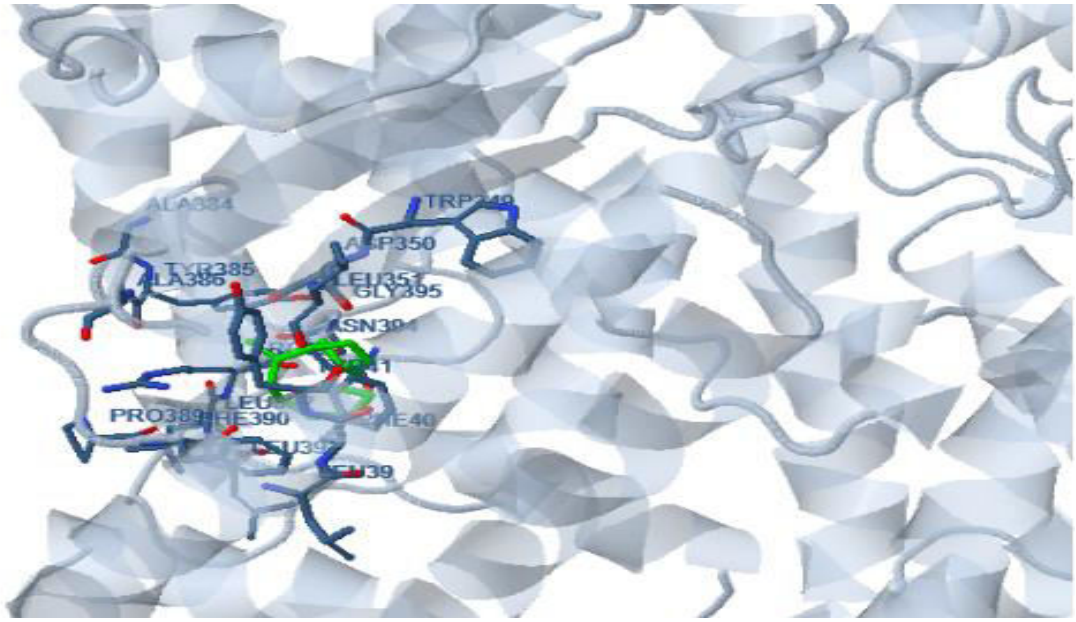


Caryophyllene with Angiotensin-converting enzyme 2 (ACE2) receptor- PDB 2AJF



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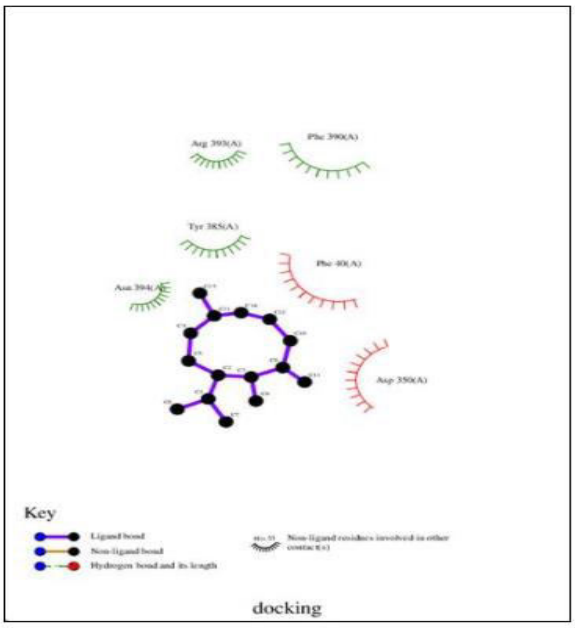

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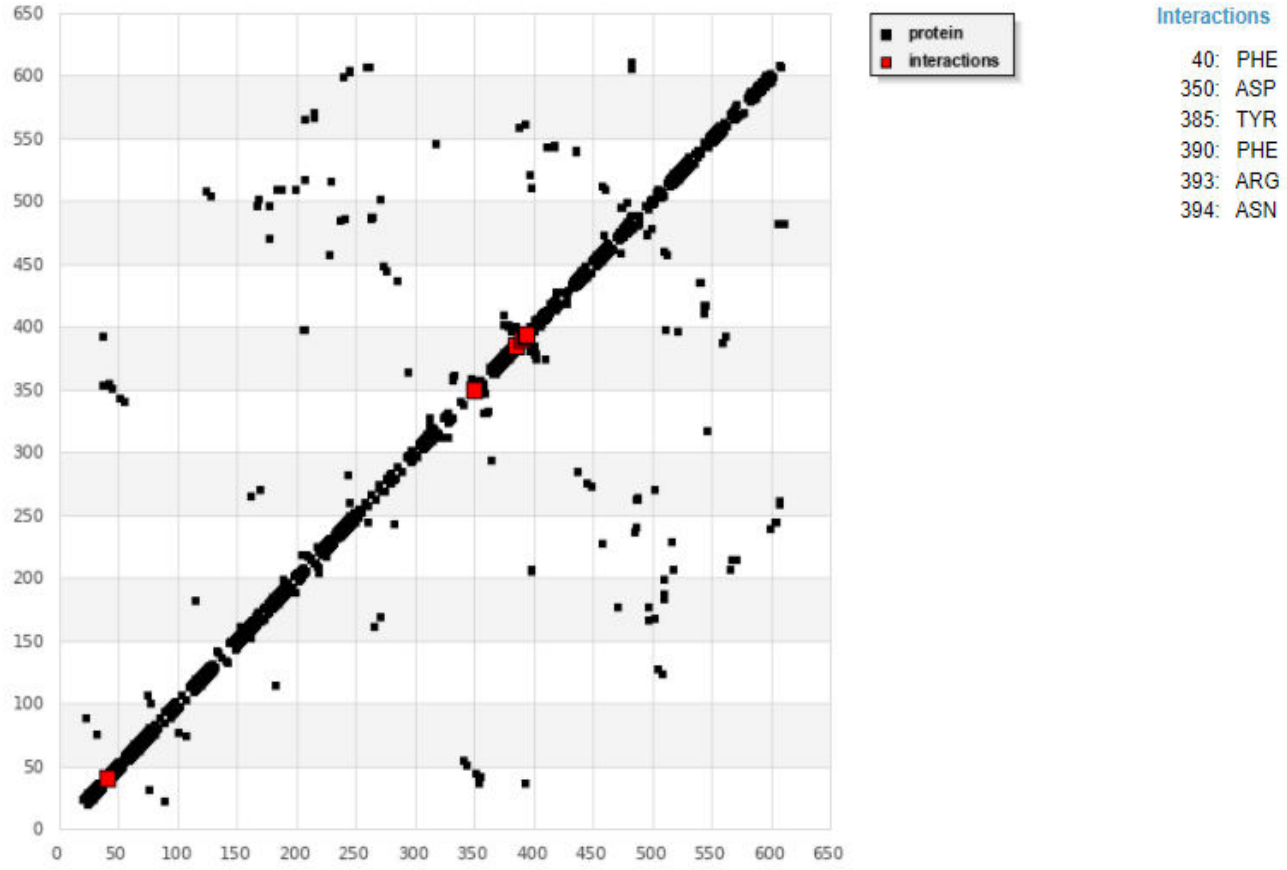
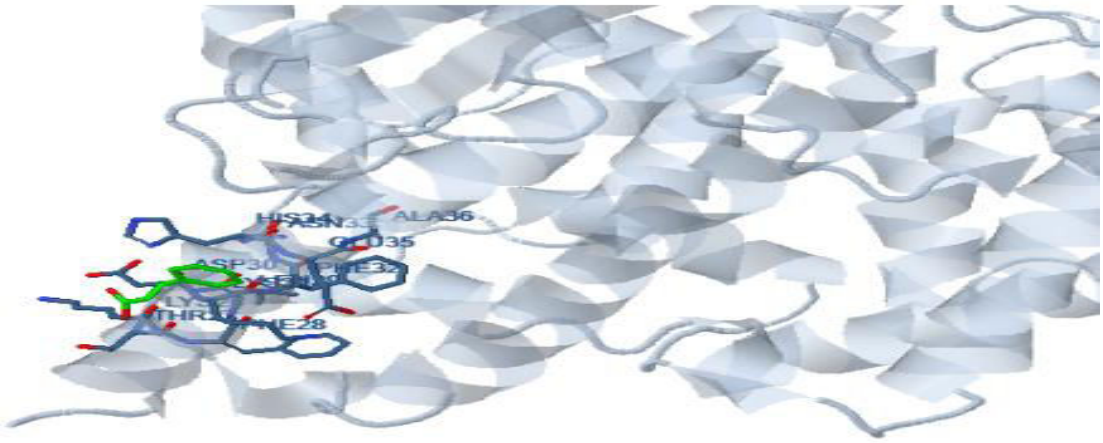


Cinnamic acid with Angiotensin-converting enzyme 2 (ACE2) receptor- PDB 2AJF



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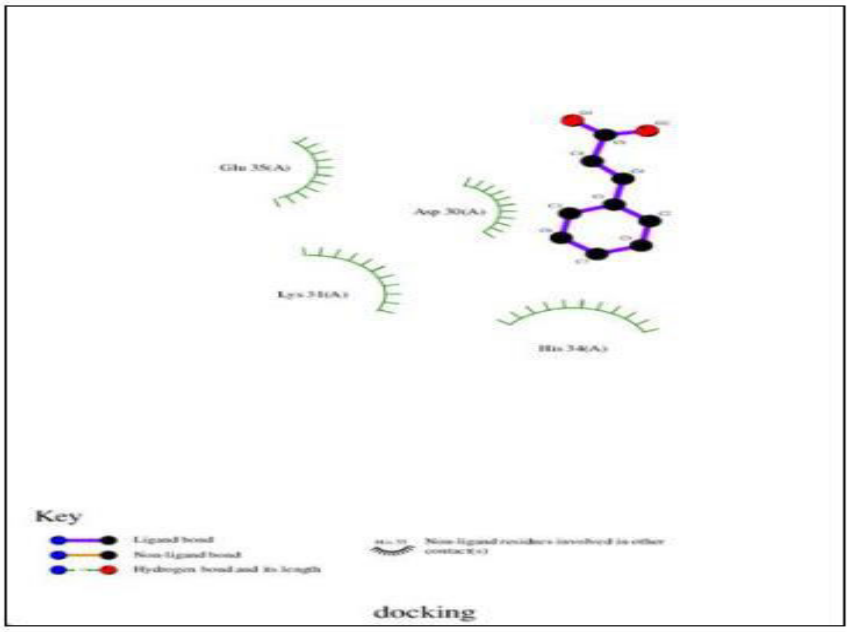
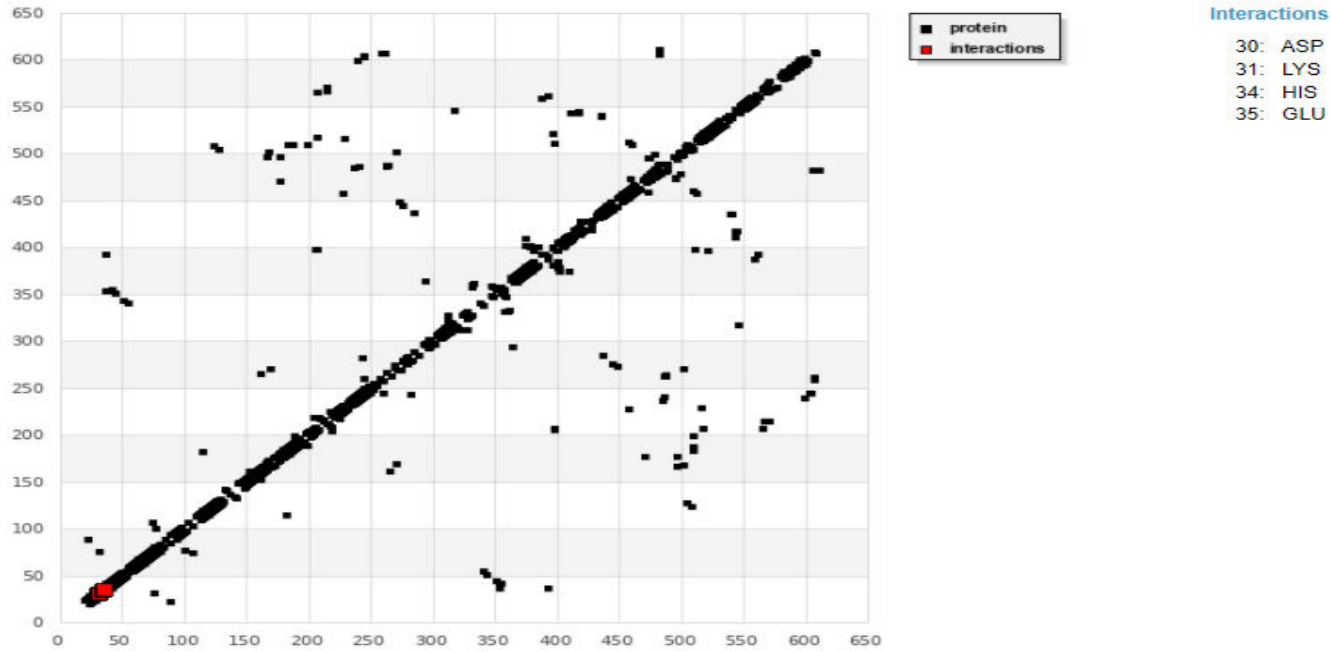


Hydrogen bond plotting with core amino acid Residues



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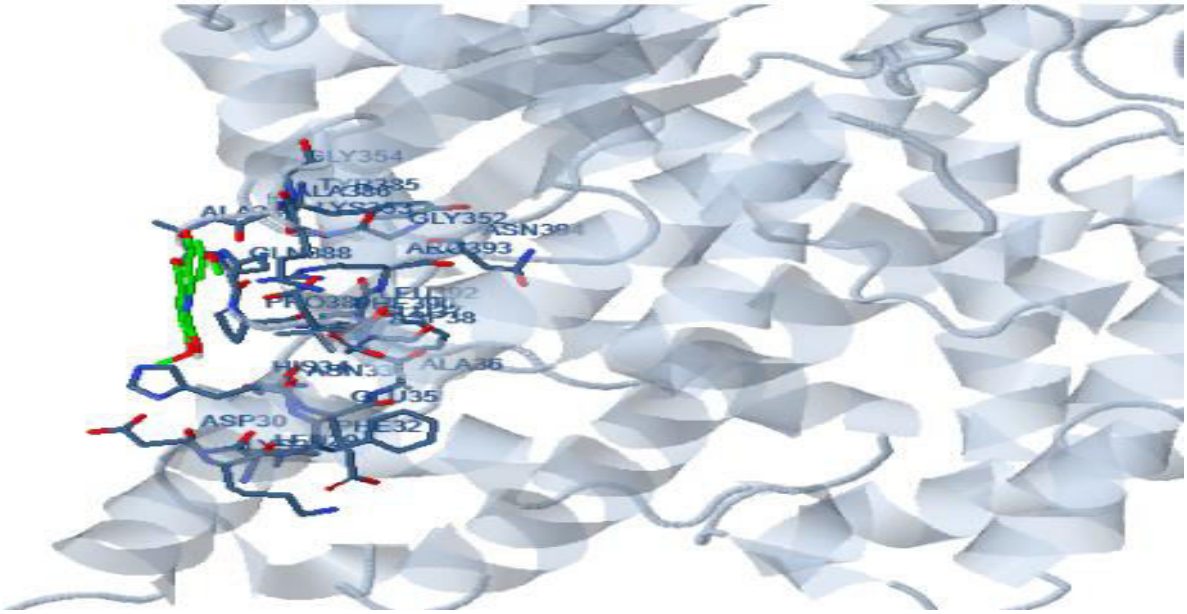
Grandisin with Angiotensin-converting enzyme 2 (ACE2) receptor- PDB 2AJF



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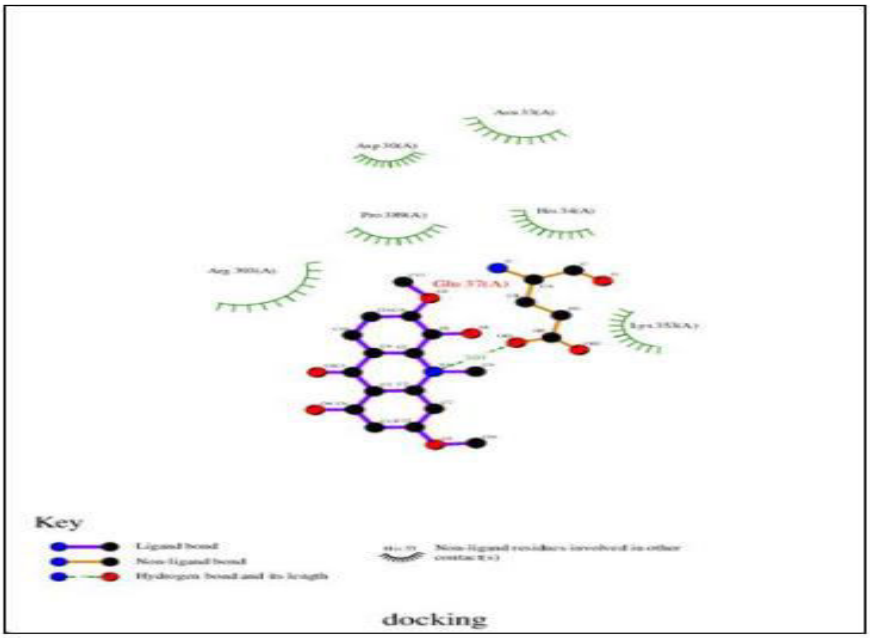

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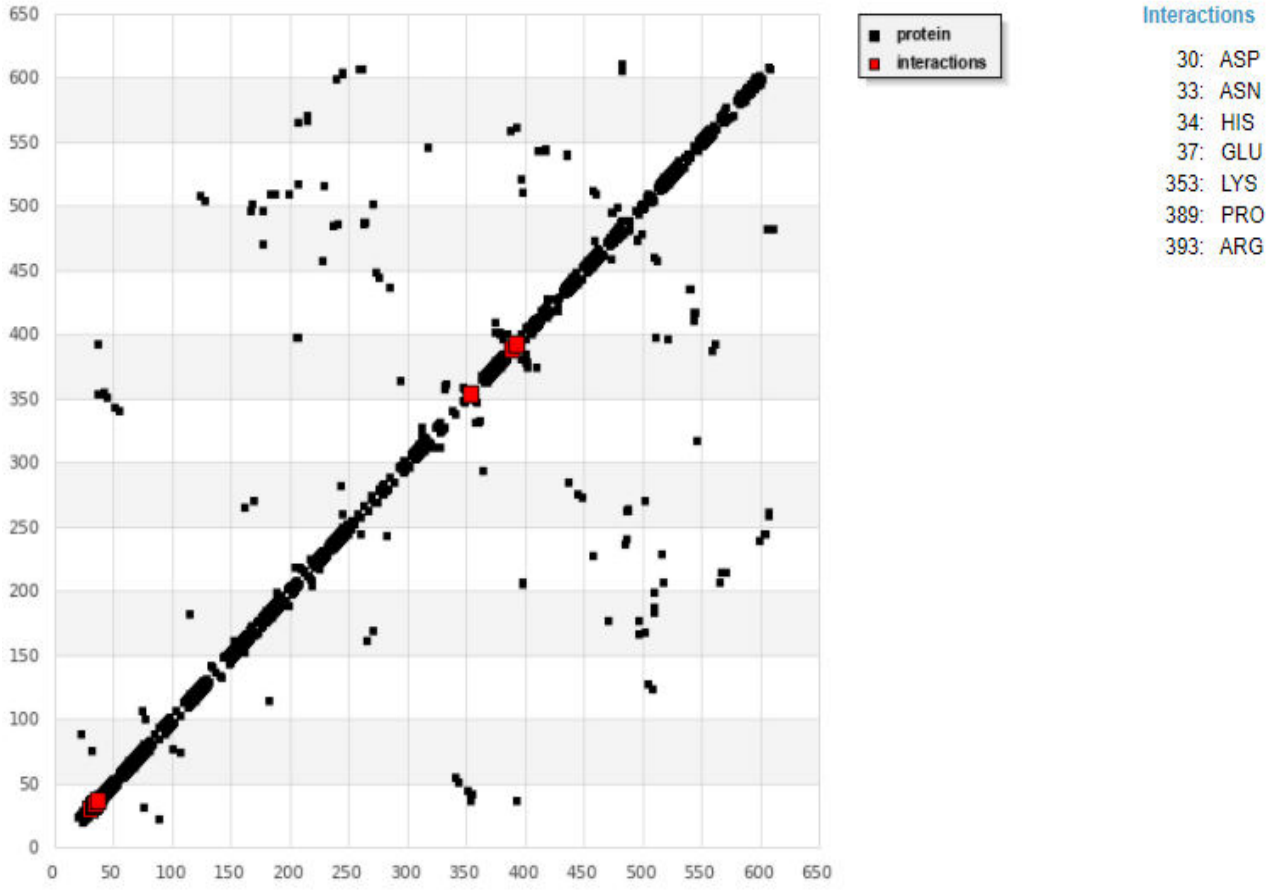

LicarinA with Angiotensin-converting enzyme 2 (ACE2) receptor-PDB 2AJF

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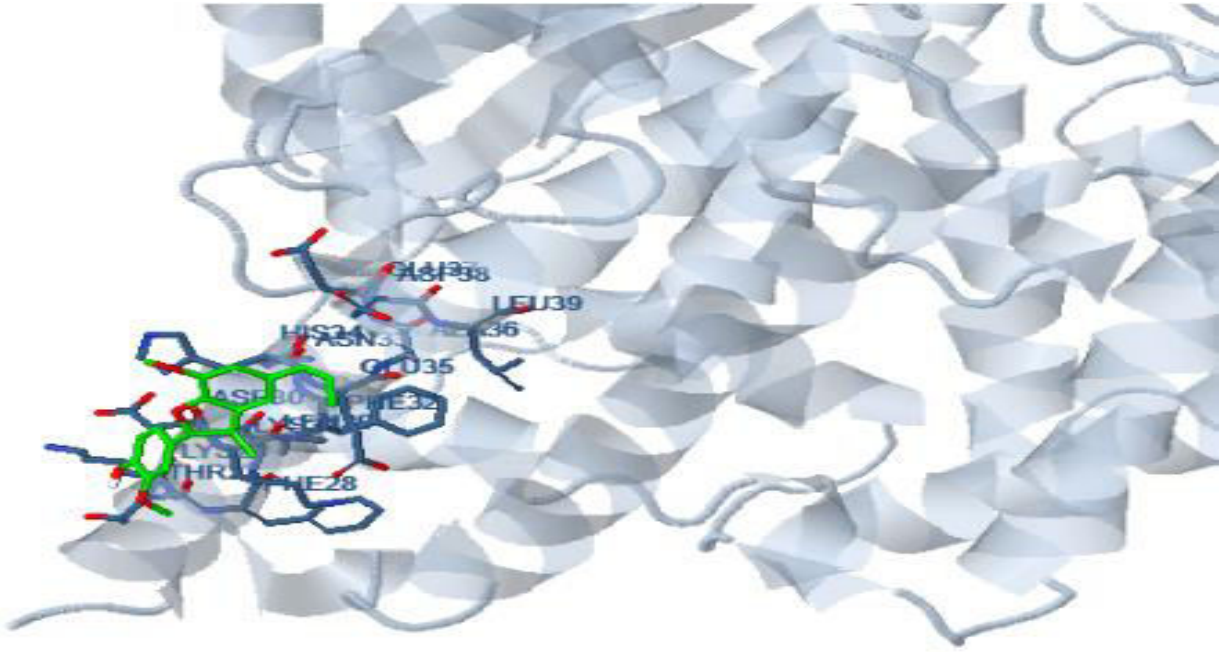

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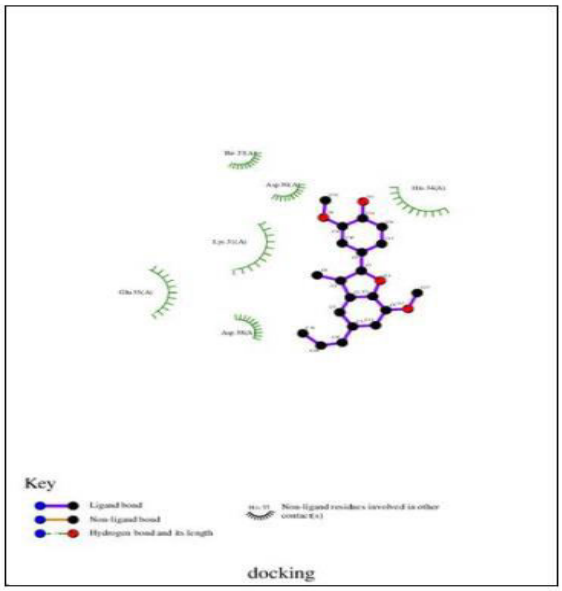

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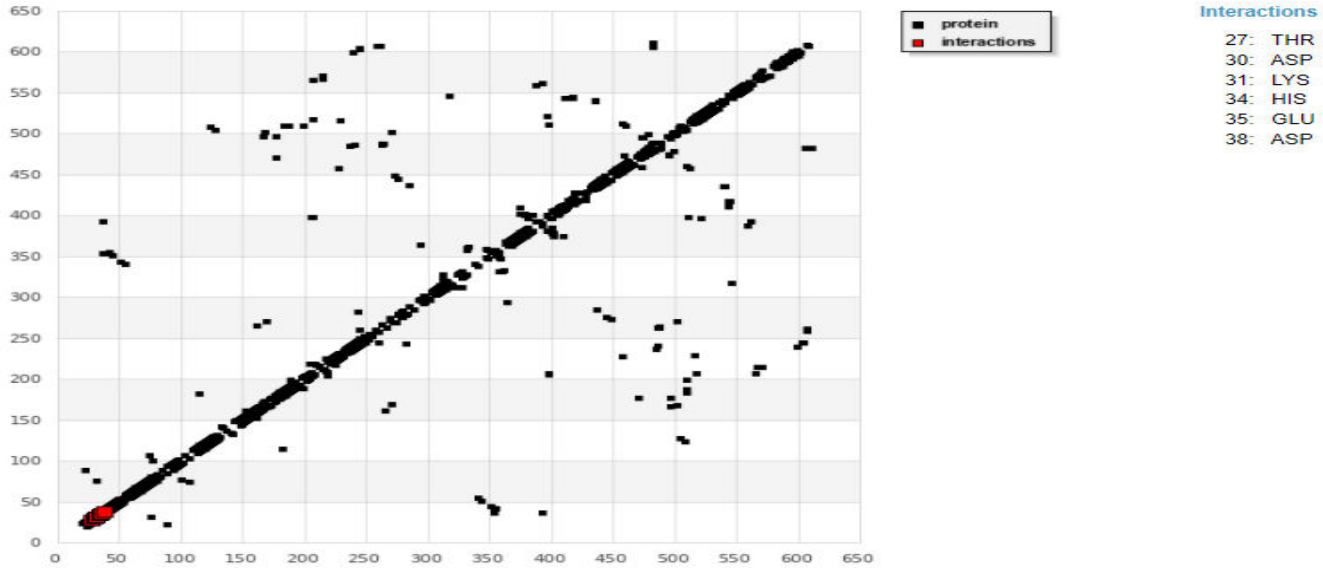

Elemicin with Angiotensin-converting enzyme 2 (ACE2) receptor- PDB 2AJF

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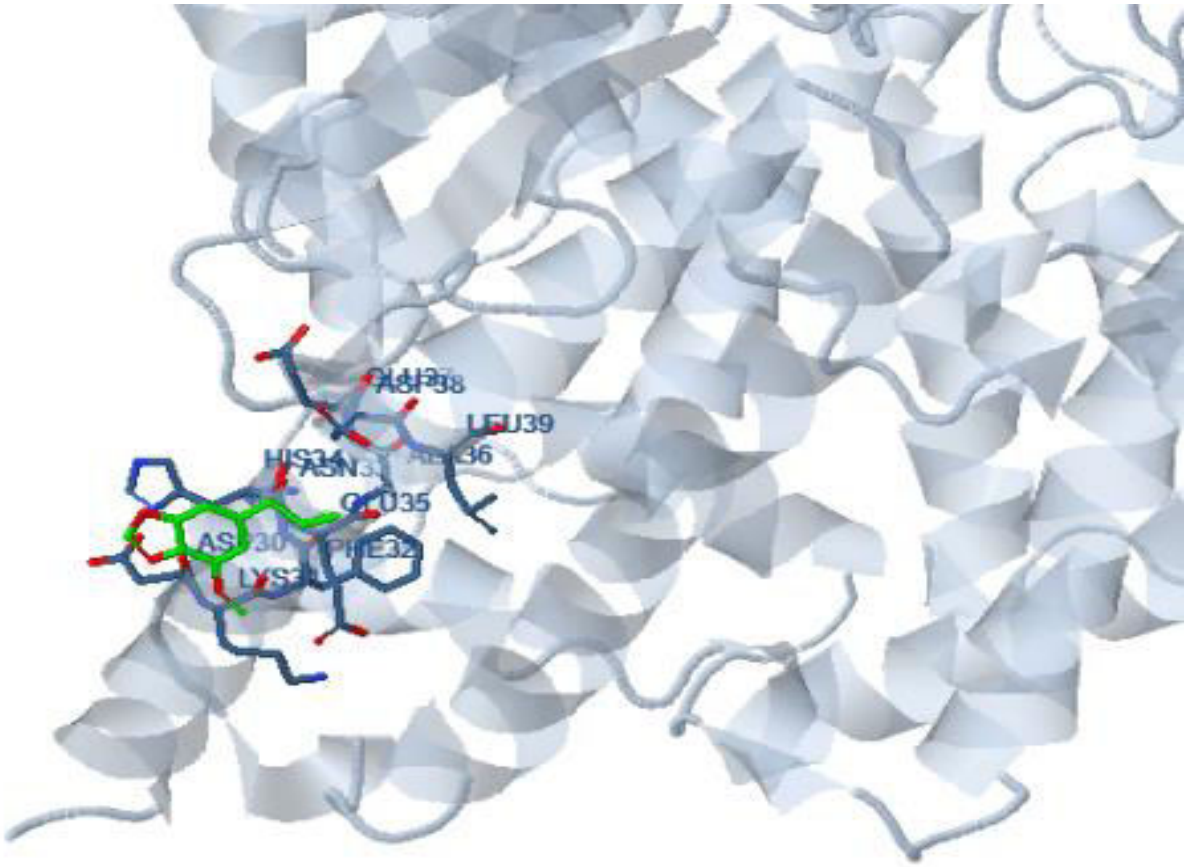

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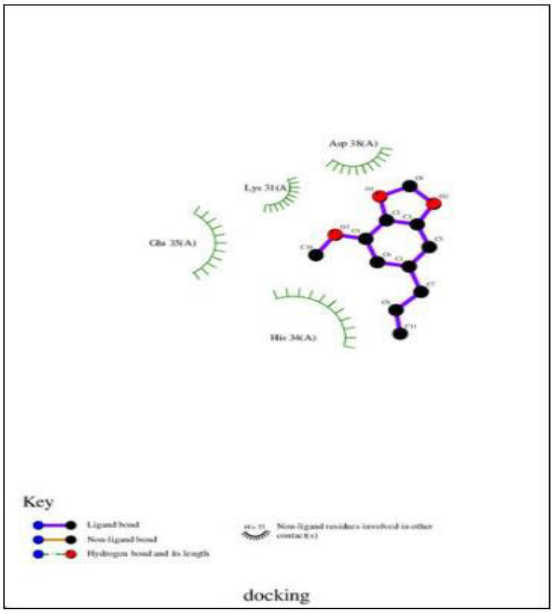

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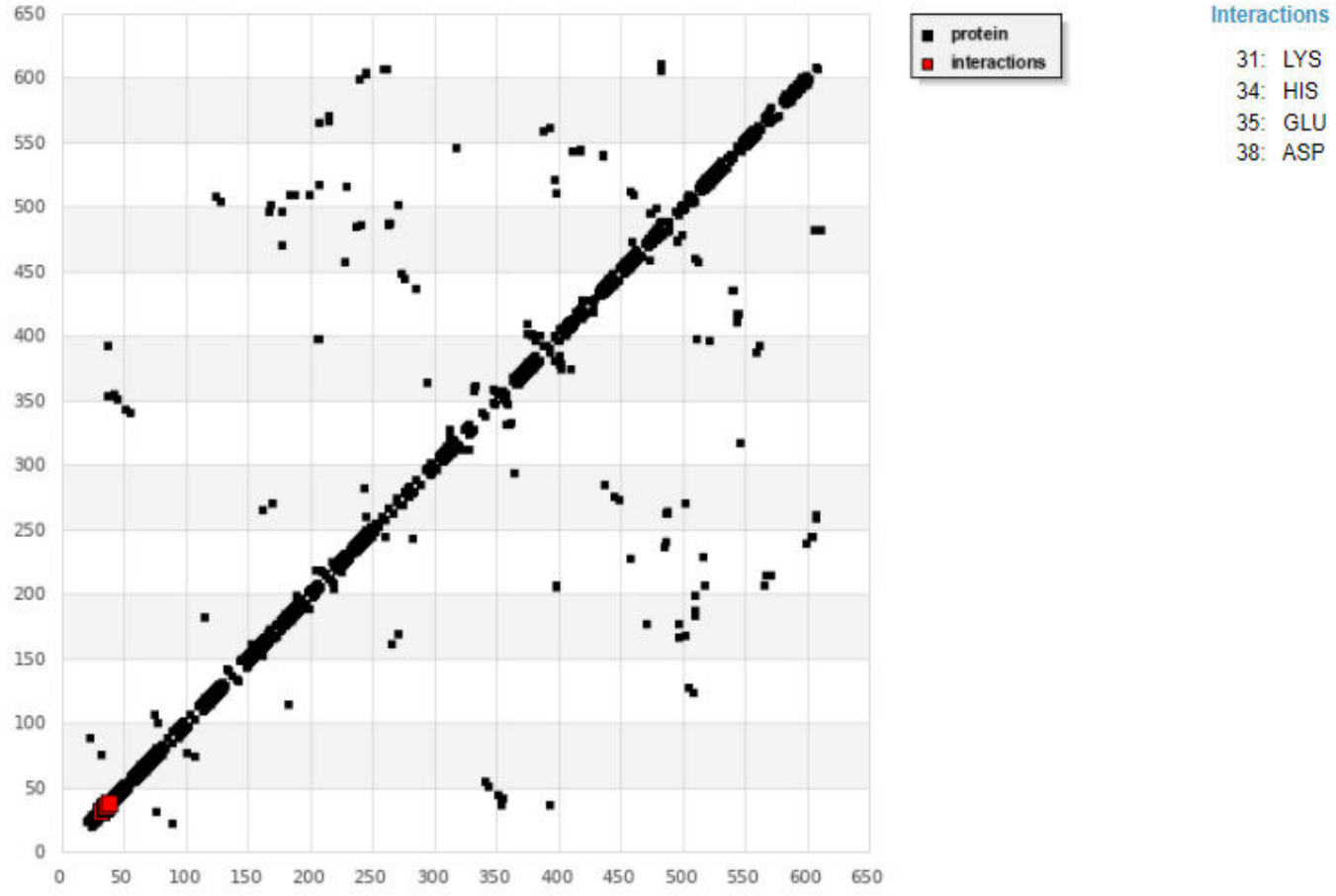

cis-Vaccenic acid with Angiotensin-converting enzyme 2 (ACE2) receptor- PDB 2AJF

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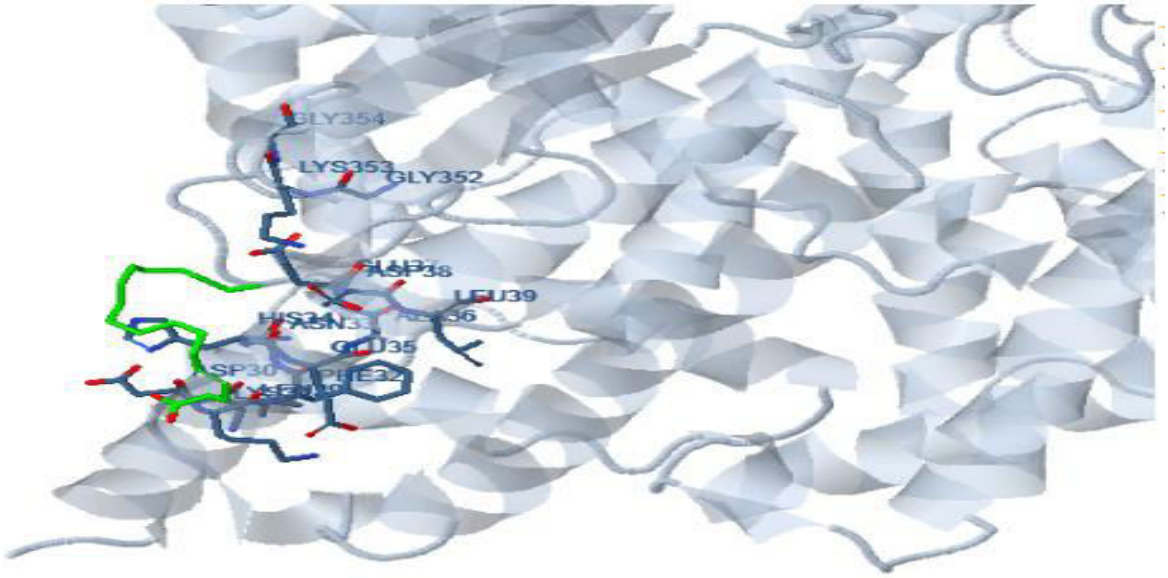
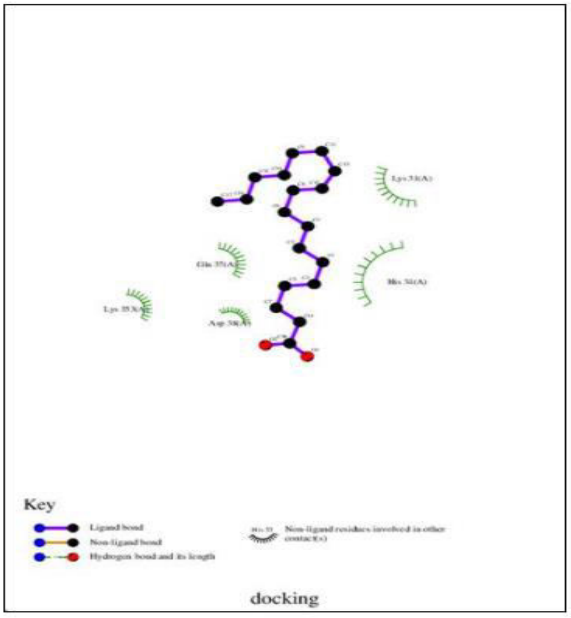


2D Interaction Plot Analysis



Hydrogen bond plotting with core amino acid Residues

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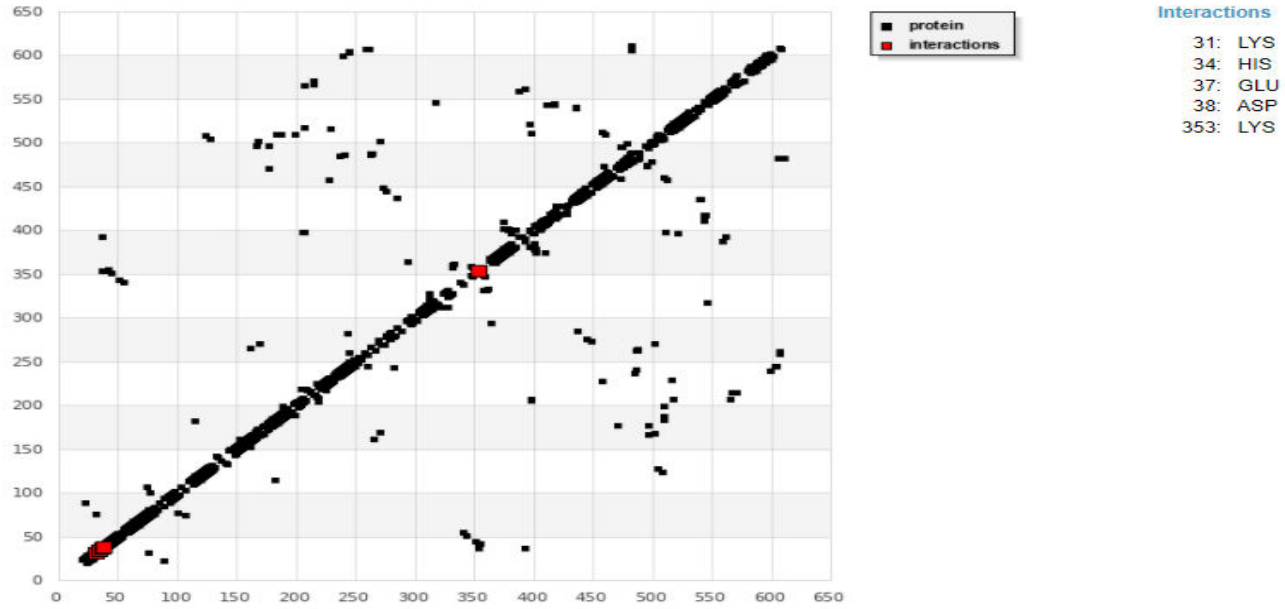
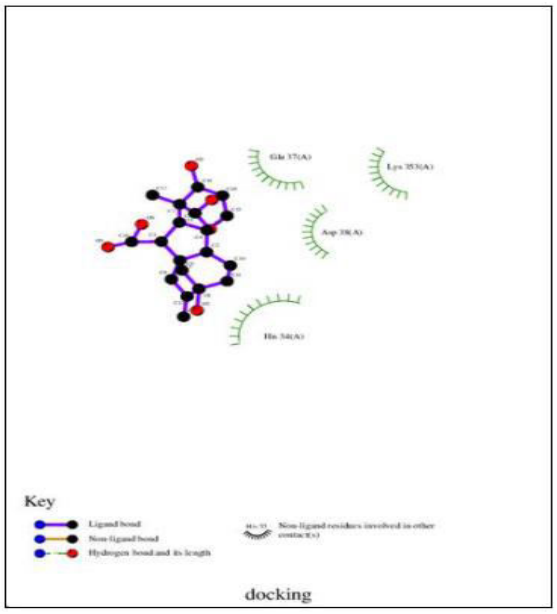


Gibberellic acid with Angiotensin-converting enzyme 2 (ACE2) receptor- PDB 2AJF

2D Interaction Plot Analysis



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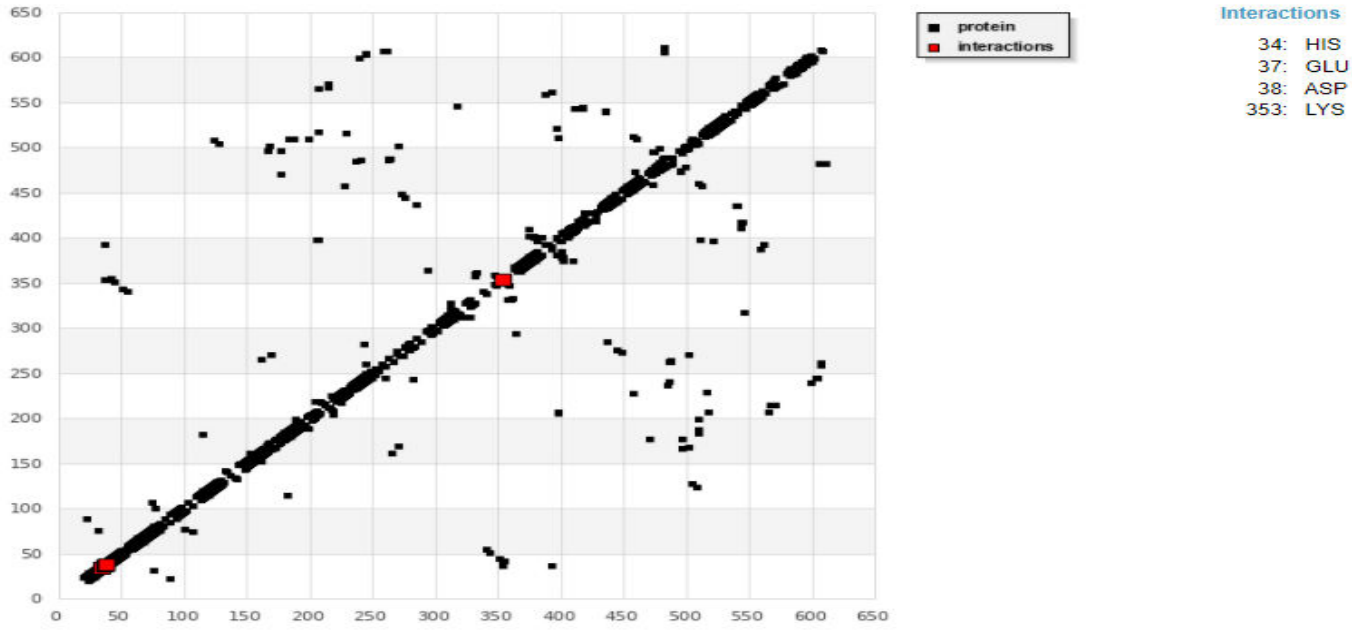
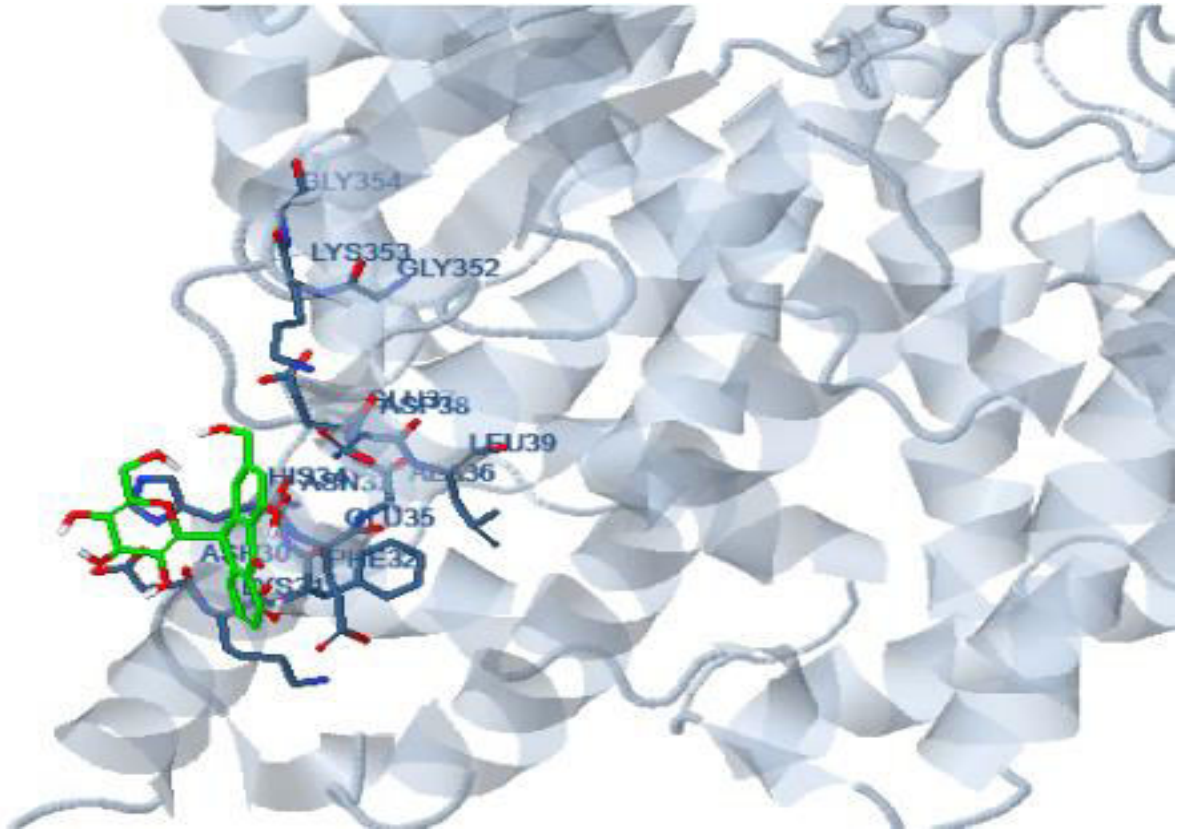


Aloin-A with Angiotensin-converting enzyme 2 (ACE2) receptor- PDB 2AJF



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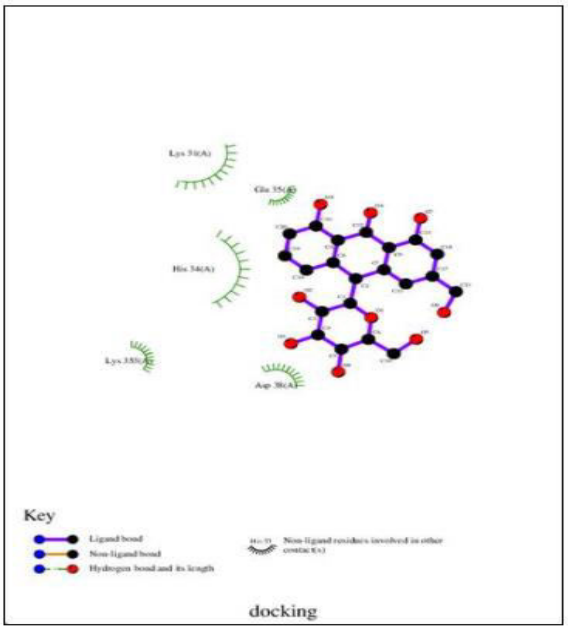

Hydrogen bond plotting with core amino acid Residues

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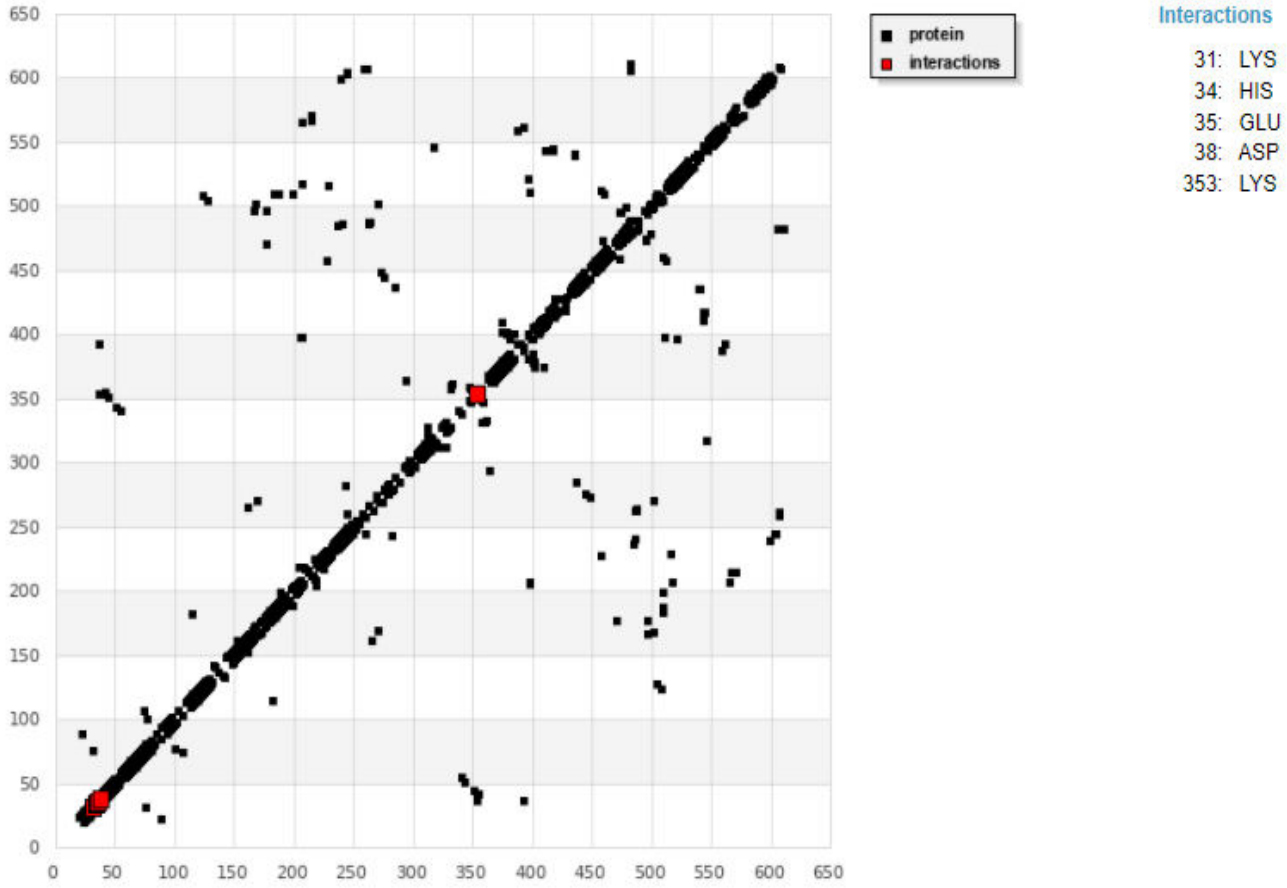
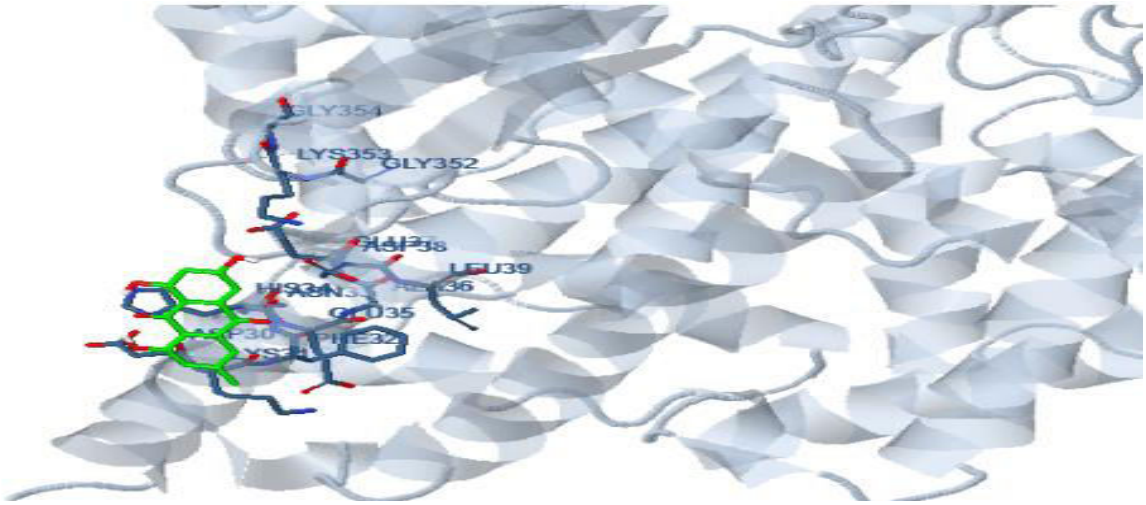


Aloe-emodin with Angiotensin-converting enzyme 2 (ACE2) receptor- PDB 2AJF



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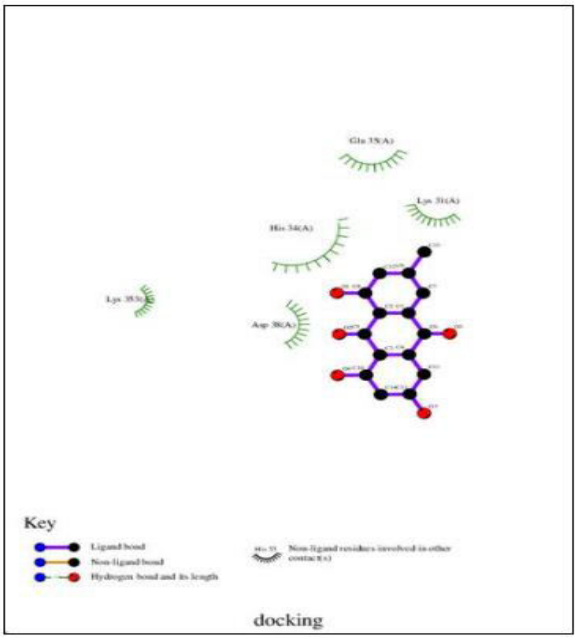
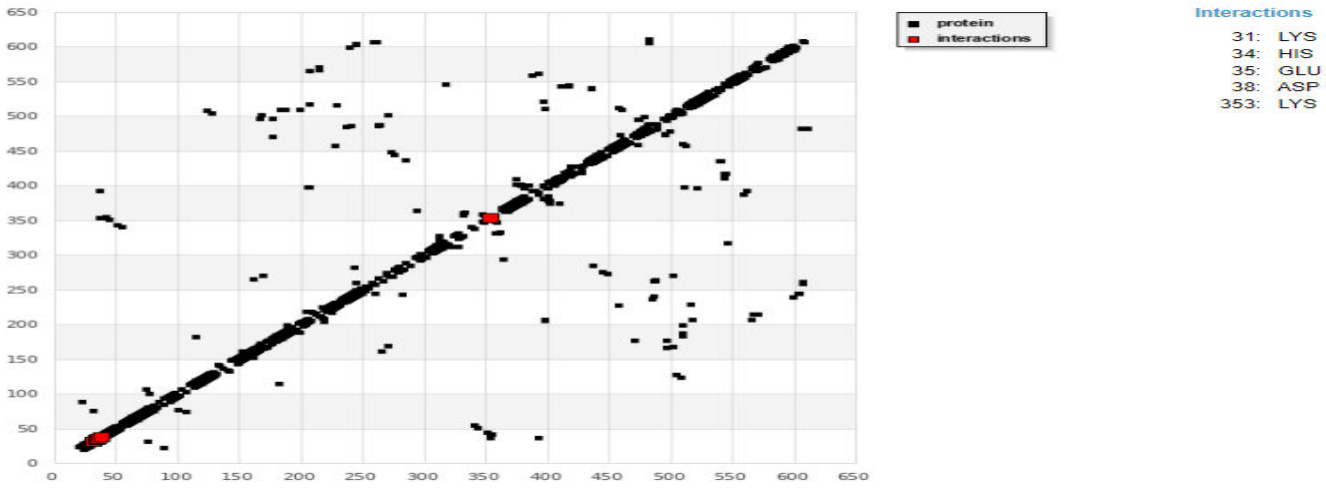
2D Interaction Plot Analysis



Hydrogen bond plotting with core amino acid Residues



Summary of the molecular docking studies of compounds against Angiotensin-converting enzyme 2 (ACE2) receptor- PDB 2AJF

Compounds	Binding Free energy Kcal/mol	Inhibition constant Ki µM	Electrostatic energy Kcal/mol	Intermolecular energy Kcal/mol	Total Interaction Surface

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		(*mM)(**nM)			
Cinnamaldehyde	-4.48	515.96	-0.01	-5.06	426.51
Caryophyllene	-5.78	58.43	-0.02	-5.78	508.86
Cinnamic acid	-3.99	1.18*	-0.63	-4.58	434.25
Grandisin	-4.58	440.75	-0.31	-4.60	449.08
LicarinA	-5.17	161.22	-0.30	-5.85	540.89
Elemicin	-4.51	497.26	-0.01	-5.35	520.36
cis-Vaccenic acid	-2.60	12.38*	-0.62	-5.89	622.20
Gibberellic acid	-4.60	421.80	-0.27	-5.49	510.95
Aloin-A	-6.77	10.38	-0.44	-5.51	567.15
Aloe-emodin	-3.93	1.31*	-0.16	-4.83	462.24

Amino acid Residue Interaction of Lead against Angiotensin-converting enzyme 2 (ACE2) receptor- PDB 2AJF

Molecules	Interaction	Amino Acid - Residue Interactions						
Cinnamaldehyde	0	40 PHE	350 ASP	390 PHE	393 ARG	394 ASN		
Caryophyllene	0	40 PHE	350 ASP	385 TYR	390 PHE	393 ARG		
Cinnamic acid	1	30 ASP	31 LYS	34 HIS	35 GLU			
Grandisin	1	30 ASP	33 ASN	34 HIS	37 GLU	353 LYS	389 PRO	393 ARG
LicarinA	1	27 THR	30 ASP	31 LYS	34 HIS	35 GLU	38 ASP	
Elemicin	1	31 LYS	34 HIS	35 GLU	38 ASP			
cis-Vaccenic acid	2	31 LYS	34 HIS	37 GLU	38 ASP	353 LYS		
Gibberellic acid	1	34 HIS	37 GLU	38 ASP	353 LYS			
Aloin-A	2	31 LYS	34 HIS	35 GLU	38 ASP	353 LYS		
Aloe-emodin	2	31 LYS	34 HIS	35 GLU	38 ASP	353 LYS		

Observation and Inference

Total of 10 bioactive lead compounds were retrieved from the herbs present in the formulations. From reported data of the herb, the lead molecules such as Vaccenic acid, Aloin-A and Aloe-emodin possess 100% binding efficacy by interacting with both the core target amino

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acids (31 LYS and 353 LYS) present on the target. Followed by this other phytocompounds such as Cinnamic acid, Grandisin, LicarinA, Elemicin and Gibberellic acid possess 50% affinity by binding with one of the target amino acid either with 31 LYS or with 353 LYS present on the target receptor ACE-2.

Conclusion

Based on the results of the computational analysis it was concluded that the bio-active compounds such as Vaccenic acid, Aloin-A and Aloe-emodin Lupeol present in the formulations revels significant binding against the target protein thereby it was concluded that these compounds may exerts promising ACE-2 receptor inhibition property and hereby halt the host-viral interface.

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