



Establishing Ligands for Tuberculosis Gene Receptor Using *In-Silico* Methods

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Abstract. *Mycobacterium tuberculosis* is a species of pathogenic bacteria of the family Mycobacteriaceae and the causative agent of tuberculosis. First discovered in 1882 by Robert Koch, *M. tuberculosis* has an unusual, waxy coating on its cell surface primarily due to the presence of mycolic acid. There are two forms tuberculosis (TB): Latent TB and Active TB. TB bacteria can live in the body without making you sick. This is called latent TB infection. People with latent TB infection: Have no symptoms. Active TB disease is a contagious. That means it can be spreads from one person to another. It is most often spread through the air. The germs may enter the air when person with TB disease of the lungs or throat cough or sneezes people nearby breathe Active in these germs and get infected. The FASTA sequence of the (genes) was retrieved from Genbank. Next, we modelled the 3d structure of the FASTA protein sequence using modeller. The best model was selected using Ramachandran plot. Phytocompounds from medicinal plants is considered *Ocimum sanctum*, *Tinospora cordifolia*, *Curcuma longa*, *Eclipta prostrate*, *Elettaria cardamomum* as considered as novel drug leads is retrieved from PUBCHEM database. The phytocompounds are checked for drug-like properties using molinspiration software. The compounds having no violation was considered for further docking studies. The phytocompounds kaempferol, fisetin, piperin having least docking score and most interactions is considered as the drug leads for Tuberculosis. Further receptor ligand binding assay studies will be done to establish the compound as drug for the above disease.

Keywords: Melioidosis, Burkholderia pseudomallei, Whitmore's disease, Bioinformatics, Docking, Phytocompound

1 Introduction

Tuberculosis (TB) is a leading cause of death worldwide. It is an infectious disease usually caused by *Mycobacterium tuberculosis* bacteria [1]. Tuberculosis is an airborne disease, spread from one person to another person through the air. It is also known as Koch's Bacillus, since Robert Koch 1st observed it in 1882 [2]. The bacterium belongs to the family mycobacteriace. *Mycobacterium* is a small, aerobic, non-motile bacillus. In nature, the bacterium can grow only within the cells of a host, but it can be cultured in the laboratory. [3]

1.1 How the genes cause the disease

NRAMP1 (Natural Resistance Associated Macrophage Protein 1) is a protein encode by the SLC11A1 gene. When a mutation of NRAMP-1 gene yields a nonfunctional NRAMP-1 protein, there is an inhibition on the intracellular killing mechanism of *M. tuberculosis* in macrophage [4].

CCL2 (C-C motif chemokine ligand-2) was evidenced to be associated with tuberculosis susceptibility in some ethnic groups [5].

A. Objectives

Computer aided drug design

In this work, the receptor gene of receptor NRAMP1 and CCL2 is taken and their 3d structure is modeled. Further, the phytochemicals from *Ocimum sanctum*, *Tinospora cordifolia*, *Curcuma longa*, *Eclipta prostrate*, *Elettaria cardamomum* are selected, screened with molinspiration based on the principles of ADME and docked with the gene receptors.

B. Abbreviations

1. et. al. : Etalia (and associate)
2. TB: Tuberculosis
3. MTB: Mycobacterium Tuberculosis
4. NCBI: National center of Biotechnology Information
5. BLAST: Basic Local Alignment Search Tool
6. FASTA: FAST-ALL
7. NRAMP1: Natural Resistance-Associated Macrophage Protein1
8. CCL2: C-C Motif Chemokine Ligand 2
9. PTB: Pulmonary Tuberculosis
10. HTS :High Throughput Sequence

2 METHODOLOGY

The FASTA sequence of the receptors NRMP-1 and CCL2) was retrieved from genbank database. Their 3d structure was modeled using modeler [6] and verified using Ramachandran Plot [7].

The SMILES of the photocompounds, *Ocimum sanctum*, *Tinospora cordifolia*, *Curcuma longa*, *Eclipta prostrate*, *Elettaria cardamomum* are retrieved from PubChem and ADME screening is done. Further, the selected compounds are docked with modeler generated best .

RESULTS

The amino acid sequence of the receptors CCL2 and NRAMP1 are retrieved and using BLAST, their homologous templates are downloaded from RCSB PDB (Table 1).

Gene receptor	Genbank accession number	Homologous templates
NRAMP1	OU343079.1	3JB9_B 7D58_D 6ZXF_F
CCL2	CP034501.1	5AOX_F 4UE5_E 7OBQ_V

The amino acid sequence of the receptors CCL2 and NRAMP1 are retrieved and using BLAST, their homologous templates are downloaded from RCSB PDB (Table 1).

Table 1: Genbank accession number of the receptors with their homologous templates

The modeler generated modes are verified using Ramachandran plot server (Table 2 and Fig. 1).

Table 2(a): Ramachandran plot analysis of CCL2

	# res in phipsi core	# res in phipsi allowed	# res in phipsi generous	# res in phipsi outside	
Model1	212 (75%)	55 (19%)	9 (3%)	3 (1%)	
Model2	228 (81%)	40 (14%)	7 (2%)	4 (1%)	
Model3	217 (77%)	48 (17%)	9 (3%)	5 (1%)	
Model4	229 (82%)	42 (15%)	5 (1%)	3 (1%)	selected
Model5	218 (78%)	53 (18%)	3 (1%)	5 (1%)	

Table 2(b): Ramachandran plot analysis of NRAMP1

	# res in phipsi core	# res in phipsi allowed	# res in phipsi generous	# res in phipsi outside	
Model1	268 (83%)	41 (12%)	10 (3%)	3 (0%)	
Model2	208 (64%)	56 (17%)	28 (8%)	30 (9%)	
Model3	248 (77%)	46 (14%)	16 (4%)	12 (3%)	
Model4	228 (70%)	61 (18%)	20 (6%)	13 (4%)	
Model5	287 (89%)	27 (8%)	3 (0%)	5 (1%)	selected

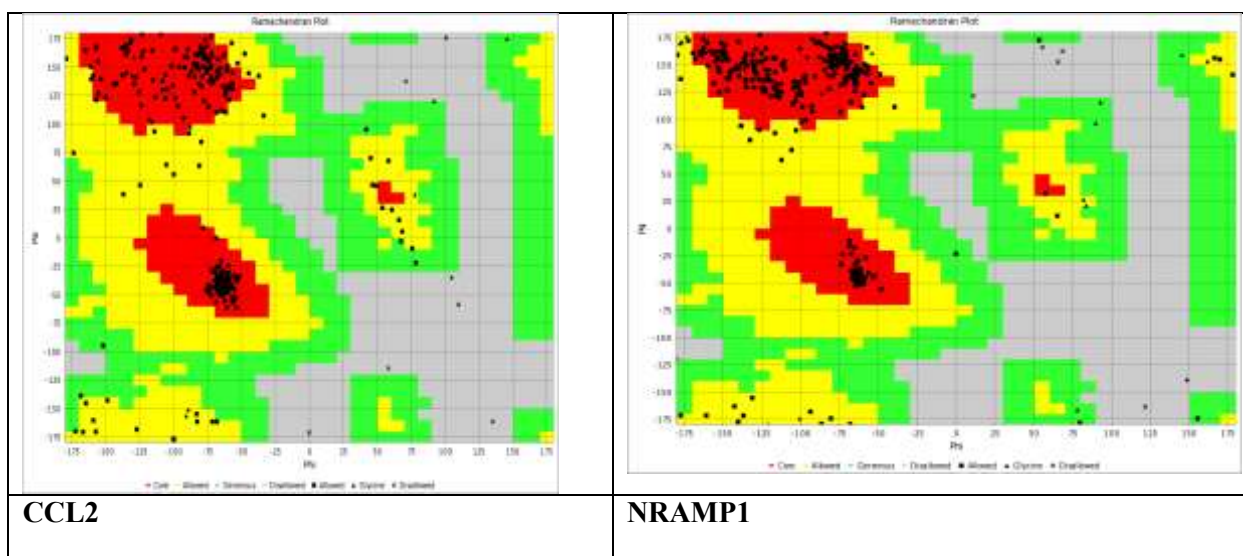


Fig. 1: Ramachandran Plot of the best model

The medicinal plants, *Ocimum sanctum*, *Tinospora cordifolia*, *Curcuma longa*, *Eclipta prostrate*, *Elettaria cardamomum* are selected and their SMILES are retrieved from PubChem (Table 3).

Table 3: **Phytochemicals and their SMILES from Pubchem**

Plant name: ocimum sanctum (Saha and Ghosh, 2012)	
Phytochemical	SMILES
Eugenol	<chem>COC1=C(C=CC(=C1)CC=C)O</chem>
Methyleugenol	<chem>COC1=C(C=C(C=C1)CC=C)OC</chem>
Methylchavicol	<chem>COC1=CC=C(C=C1)CC=C</chem>
Beta-Elemene	<chem>CC(=C)C1CCC(C(C1)C(=C)C)(C)C=C</chem>
Beta-caryophyllene	<chem>CC1=CCCC(=C)C2CC(C2CC1)(C)C</chem>
Caryophyllene oxide	<chem>CC1(CC2C1CCC3(C(O3)CCC2=C)C)C</chem>
Isocaryophyllene	<chem>CC1=CCCC(=C)C2CC(C2CC1)(C)C</chem>

Plant name: Tinospora cordifolia (Pattanayak et.al., 2010)	
Phytochemical	SMILES
Eugenol	<chem>COC1=C(C=CC(=C1)CC=C)O</chem>
Carvacrol	<chem>CC1=C(C=C(C=C1)C(C)C)O</chem>
Linalool	<chem>CC(=CCCC(C)(C=C)O)C</chem>

Plant name: curcuma longa (Ammon andWahl, 1991)	
Phytochemicals	SMILES
Myricetin	<chem>C1=C(C=C(C(=C1O)O)O)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O</chem>
Quercetin	<chem>CC1C(C(C(C(O1)OC2=C(OC3=CC(=CC(=C3C2=O)O)O)C4=CC(=C(C=C4)O)O)O)O)O</chem>
Vasicine	<chem>C1CN2CC3=CC=CC=C3N=C2C1O</chem>
Piperine	<chem>C1CCN(CC1)C(=O)C=CC=CC2=CC3=C(C=C2)OCO3</chem>
Ascorbic acid	<chem>C(C(C1C(=C(C(=O)O1)O)O)O)O</chem>

Plant name: Eclipta prostrate (Feng et.al, 2019)	
Phytochemicals	SMILES
Quercetin	<chem>CC1C(C(C(C(O1)OC2=C(OC3=CC(=CC(=C3C2=O)O)O)C4=CC(=C(C=C4)O)O)O)O)O</chem>
(-)-epicatechin	<chem>C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O</chem>
(-)epigallocatechin	<chem>C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)OC(=O)C4=CC(=C(C=C4)O)O)O</chem>
Kaempferol	<chem>C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O</chem>
Luteolin	<chem>C1=CC(=C(C=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O)O</chem>
Fisetin	<chem>C1=CC(=C(C=C1C2=C(C(=O)C3=C(O2)C=C(C=C3)O)O)O)O</chem>

Plant name: <i>Elettaria cardamomum</i> (Yahyazadeh et.al, 2011)	
Phytochemicals	SMILES
Alpha-terpinyl acetate	<chem>CC1=CCC(CC1)C(C)(C)OC(=O)C</chem>
1,8-cineole	<chem>CC1(C2CCC(O1)(CC2)C)C</chem>
Alpha-terpineol	<chem>CC1=CCC(CC1)C(C)(C)O</chem>
Linalyl acetate	<chem>CC(=CCCC(C)(C=C)OC(=O)C)C</chem>
Terpinen-4-ol	<chem>CC1=CCC(CC1)C(C)C)O</chem>
Beta-pinen	<chem>CC1(C2CCC(=C)C1C2)C</chem>
Beta-selinene	<chem>CC(=C)C1CCC2(CCCC(=C)C2C1)C</chem>

Further, using molinspiration their drug- like properties are identified and screened based on no violations from Lipinski's rule of five (Table 4).

Table 4: ADME property detection of phytochemicals using molinspiration (molinspiration)

Phytochemicals	mil.logP	TPSA	natoms	MW	nON	nOHNH	nrotb	volume	nviolation
Eugenol	2.10	29.46	12	164.20	2	1	3	162.14	0
methyleugenol	2.41	18.47	13	178.23	2	0	4	179.67	0
methylchavicol	2.82	9.23	11	148.21	1	0	3	154.12	0
Beta-Elementene	5.37	0.00	15	204.36	0	0	3	235.23	1
Beta-caryophyllene	5.17	0.00	15	204.36	0	0	0	229.95	1
Caryophyllene oxide	4.14	12.53	16	220.36	1	0	0	234.01	0
Isocaryophyllene	5.17	0.00	15	204.36	0	0	0	229.95	1
Eugenol	2.10	29.46	12	164.20	2	1	3	162.14	0
carvacrol	3.81	20.23	11	150.22	1	1	1	158.57	0
Linalool	3.21	20.23	11	154.25	1	1	4	175.59	0
myricetin	1.39	151.58	23	318.24	8	6	1	248.10	1
Quercetin	0.64	190.28	32	448.38	11	7	3	363.95	2
Vasicine	1.04	35.83	14	188.23	3	1	0	173.66	0
Piperine	3.33	38.78	21	285.34	4	0	3	267.74	0
Ascorbic acid	-1.40	107.22	12	176.12	6	4	2	139.71	0
Quercetin	0.64	190.28	32	448.38	11	7	3	363.95	2
(-)-epicatechin	1.37	110.37	21	290.27	6	5	1	244.14	0
(-)-epigallocatechin	2.25	197.36	33	458.38	11	8	4	367.57	4
kaempferol	2.17	111.12	21	286.24	6	4	1	232.07	0
Luteolin	1.97	111.12	21	286.24	6	4	1	232.07	0
Fisetin	1.97	111.12	21	286.24	6	4	1	232.07	0
Alpha-terpinyl acetate	3.30	26.30	14	196.29	2	0	3	207.16	0
1,8-cineole	2.72	9.23	11	154.25	1	0	0	166.66	0
Alpha-terpineol	2.60	20.23	11	154.25	1	1	1	170.65	0
Linalyl acetate	3.92	26.30	14	196.29	2	0	6	212.10	0
Terpinen-4-ol	2.60	20.23	11	154.25	1	1	1	170.65	0
Beta-pinen	3.33	0.00	10	136.24	0	0	0	152.37	0
Beta-selinene	5.02	0.00	15	204.36	0	0	1	230.51	1

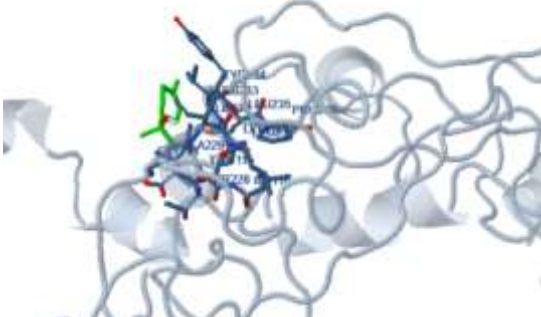

The phytochemicals having nviolations 0 are considered for further docking studies (Bikadi and Hazai, 2009) (Table 5). The phytochemicals are docked with best receptor models selected above in Table 2 and 3.

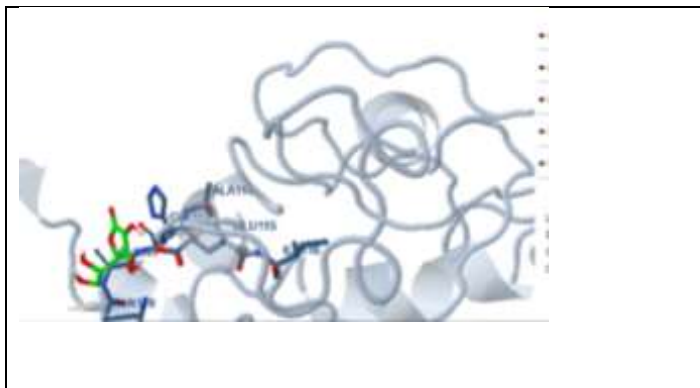
Table 5(a): Docking studies of CCL2.D99990004

Phyto-compound	Docking score	No. of interactions	Docking (yes/no)
Alpha-terpineol	-4.95kcal/mol	8	Yes
Alpha-terpinyl acetate	-4.10kcal/mol	7	Yes
Ascorbic acid	-2.87kcal/mol	14	Yes
Beta-pinen	-4.07kcal/mol	6	Yes
Carvacrol	-4.50kcal/mol	11	Yes
Caryophyllene oxide	-4.82kcal/mol	13	Yes

Eugenol	-3.91kcal/mol	11	Yes
Fisetin	-4.84kcal/mol	16	Yes
Kaempferol	-4.65kcal/mol	19	Yes
Linalool	-3.57kcal/mol	14	Yes
Linalyl acetate	-4.03kcal/mol	14	Yes
Luteolin	-4.67kcal/mol	20	Yes
Methylchavicol	-3.93kcal/mol	10	Yes
Methyleugenol	-4.59kcal/mol	10	Yes
Piperin	-5.04kcal/mol	15	Yes
Terpinen-4-ol	-4.11kcal/mol	7	Yes
Vasicine	-3.57kcal/mol	11	Yes

Table 5(b): Docking images and their interacted amino acid residues.

	<table border="1"> <thead> <tr> <th colspan="2">hydrophobic</th> <th colspan="2">other</th> </tr> </thead> <tbody> <tr> <td>C7 (1)</td> <td>- ALA114 (146)</td> <td>C8 (1)</td> <td>- GLU115 (146)</td> </tr> <tr> <td>C9 (1)</td> <td>- LEU233 (146)</td> <td>O1 (0)</td> <td>- ALA229 (146)</td> </tr> <tr> <td>C10 (0)</td> <td>- TYR234 (146)</td> <td>H1 (1)</td> <td>- ALA229 (146)</td> </tr> <tr> <td></td> <td></td> <td>H1 (1)</td> <td>- LEU233 (146)</td> </tr> <tr> <td></td> <td></td> <td>O1 (0)</td> <td>- LEU233 (146)</td> </tr> </tbody> </table>	hydrophobic		other		C7 (1)	- ALA114 (146)	C8 (1)	- GLU115 (146)	C9 (1)	- LEU233 (146)	O1 (0)	- ALA229 (146)	C10 (0)	- TYR234 (146)	H1 (1)	- ALA229 (146)			H1 (1)	- LEU233 (146)			O1 (0)	- LEU233 (146)
hydrophobic		other																							
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		O1 (0)	- LEU233 (146)																						
<p>Alpha-terpineol-docking</p>	<p>Alpha-terpineol docking interacting amino acids</p>																								
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<p>Alpha-terpinyl acetate docking</p>	<p>Alpha-terpinyl acetate docking interacting amino acids</p>																								



Ascorbic acid docking

Interaction Table		
hydrogen bonds	polar	other
O(1) - ALA110 [14] - H	O(1) - GLY115 [14] - H	O(1) - GLY115 [14] - [14-OR]
	O(1) - GLY115 [14] - [14]	O(1) - GLY115 [14] - [14]
	H(1) - GLY115 [14] - [14]	O(1) - GLY115 [14] - [14]
	O(1) - GLY115 [14] - [14]	H(1) - GLY115 [14] - [14-OR]
	H(1) - GLY115 [14] - [14]	H(1) - GLY115 [14] - [14]
		O(1) - GLY115 [14] - [14]
		O(1) - GLY115 [14] - [14]

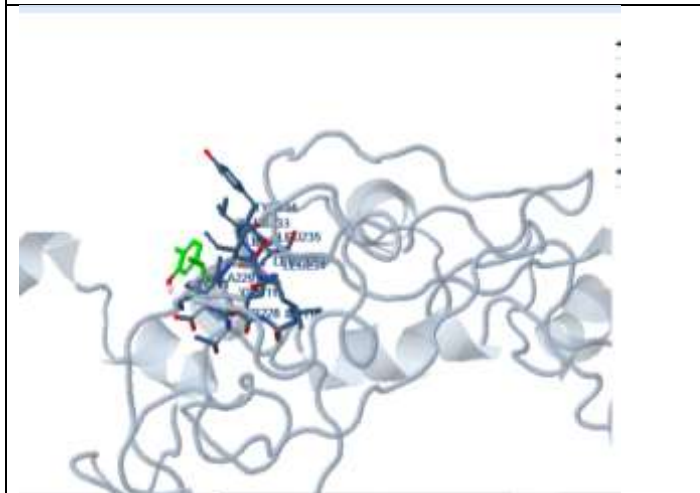
Ascorbic acid docking interacting amino acids



Beta-pinene docking

Interaction Table		
hydrophobic	other	
O(1) - ALA228 [14] - [14]	O(1) - GLY115 [14] - [14]	
O(1) - LEU232 [14] - [14]	O(1) - GLY115 [14] - [14]	
	O(1) - GLY115 [14] - [14]	
	O(1) - GLY115 [14] - [14]	

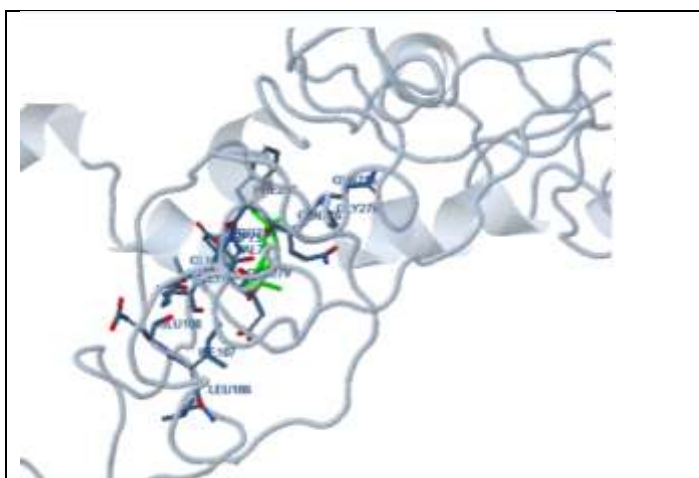
Beta-pinene docking interacting amino acids



Carvacrol docking

Interaction Table		
polar	hydrophobic	other
O(1) - GLY115 [14] - [14]	O(1) - ALA110 [14] - [14]	O(1) - GLY115 [14] - [14-OR]
H(1) - GLY115 [14] - [14]	O(1) - ALA110 [14] - [14]	O(1) - GLY115 [14] - [14-OR]
	O(1) - ALA228 [14] - [14]	O(1) - GLY115 [14] - [14-OR]
	O(1) - LEU232 [14] - [14]	O(1) - GLY115 [14] - [14-OR]
		H(1) - GLY115 [14] - [14-OR]

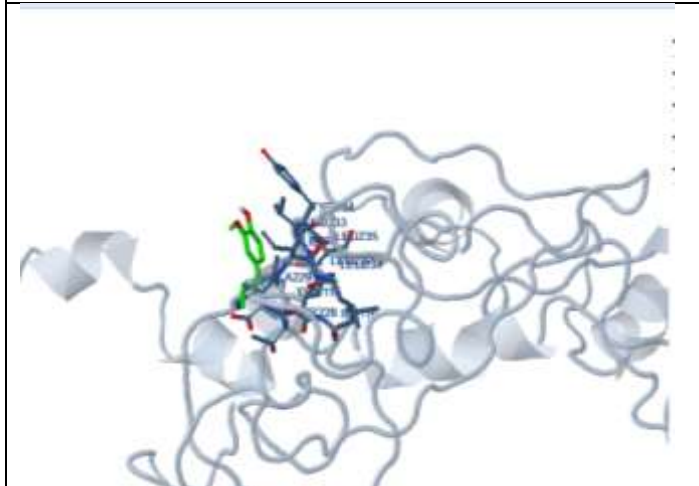
Carvacrol docking interacting amino acids



Interaction Table			
hydrophobic		other	
C11 - ARG227	D16 - O01	C11 - ASP75	D16 - O01
C12 - ARG227	D16 - O01	C11 - ASP75	D16 - O01
C11 - ARG276	D16 - O01 O1	C11 - ASP75	D16 - O01
C12 - ARG276	D16 - O01	C11 - LEU7	D16 - O01
C11 - ARG276	D16 - O01 O1	C11 - GLN78	D16 - O01 O1
C11 - ARG276	D16 - O01 O1	C11 - GLN78	D16 - O01
C11 - ARG276	D16 - O01 O1		

Caryophyllene oxide docking

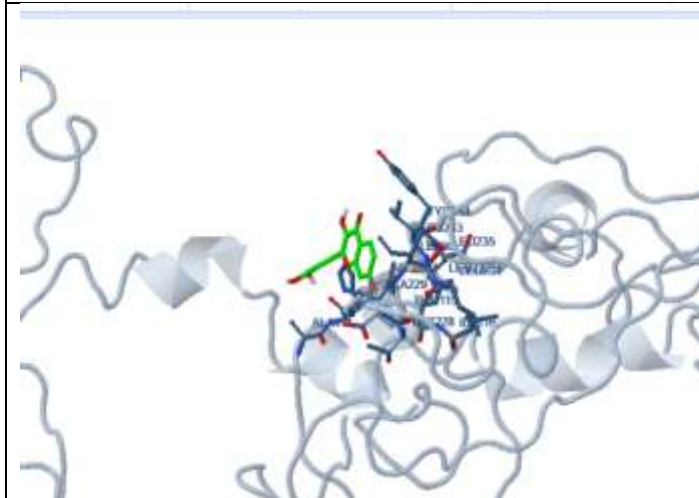
Caryophyllene oxide docking interacting amino acids



Interaction Table			
hydrophobic		other	
C11 - ARG227	D16 - O01	C11 - GLN78	D16 - O01
C12 - ARG227	D16 - O01	C11 - GLN78	D16 - O01 O1
C11 - LEU233	D16 - O01	C11 - GLN78	D16 - O01 O1
C11 - LEU233	D16 - O01	C11 - GLN78	D16 - O01 O1
C11 - LEU233	D16 - O01	C11 - LEU233	D16 - O01
		ASP75 - LEU233	D16 - O01

Eugenol docking

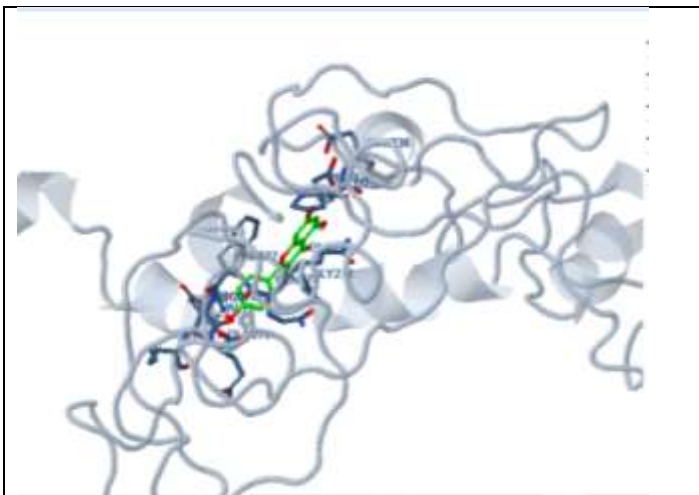
Eugenol docking interacting amino acids



Interaction Table			
other	hydrophobic	other	
C11 - GLN78	C11 - ARG227	H71 - GLN78	D16 - O01
H71 - GLN78	C11 - ARG227	C11 - GLN78	D16 - O01
C11 - GLN78	C11 - ARG227	C11 - GLN78	D16 - O01
H71 - GLN78	C11 - ARG227	H71 - GLN78	D16 - O01
		C11 - GLN78	D16 - O01
		C11 - GLN78	D16 - O01
		C11 - ARG227	D16 - O01
		C11 - ASP75	D16 - O01

Fisetin docking

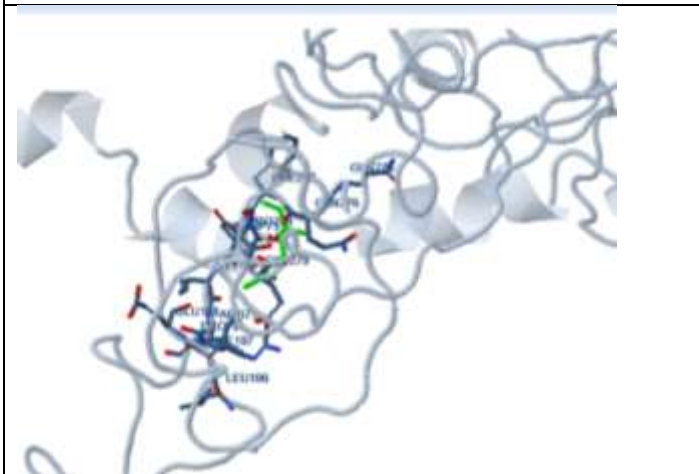
Fisetin docking interacting amino acids



Kaempferol docking

Interaction Table			
polar	hydrophobic	pi-pi	other
O1 () - ASP100 [14] - O21	C5 () - PRO176 [14] - O2 - O21	O2 () - PHE177 [14] - O21	H10 () - ASP100 [14] - O21
H10 () - ASP103 [14] - O21	C14 () - PRO176 [14] - O2 - O21	O2 () - PHE177 [14] - O21	C15 () - ASP103 [14] - O21
O5 () - GLN107 [14] - O21		O8 () - PHE177 [14] - O21 - O21 - O21	C14 () - ASP103 [14] - O21
H8 () - GLN107 [14] - O21			O5 () - GLN107 [14] - O21 - O21 - O21
O5 () - GLN105 [14] - O21			H8 () - GLN107 [14] - O21 - O21 - O21
H8 () - GLN105 [14] - O21			O5 () - GLN105 [14] - O21
			O5 () - GLN105 [14] - O21 - O21 - O21
			O8 () - GLN105 [14] - O21

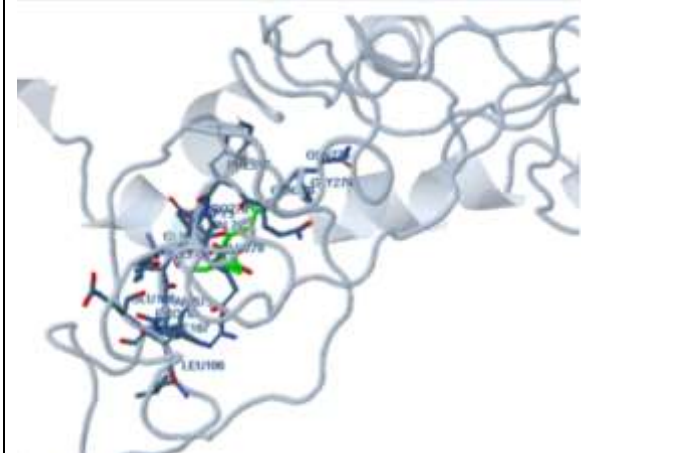
Kaempferol docking interacting amino acids



Linalool docking

Interaction Table		
polar	hydrophobic	other
O1 () - ASP100 [14] - O21	O8 () - LEU107 [14] - O21	H10 () - ASP100 [14] - O21
H10 () - ASP103 [14] - O21	O2 () - PRO176 [14] - O2 - O21	C16 () - ASP103 [14] - O21 - O21 - O21
	O5 () - PRO176 [14] - O21	O7 () - ASP103 [14] - O21
	C11 () - PRO176 [14] - O2 - O21	C1 () - ASP103 [14] - O21
	O5 () - PRO176 [14] - O2 - O21	O2 () - ASP103 [14] - O21 - O21 - O21
		C1 () - GLN105 [14] - O21 - O21 - O21
		H10 () - PRO176 [14] - O21

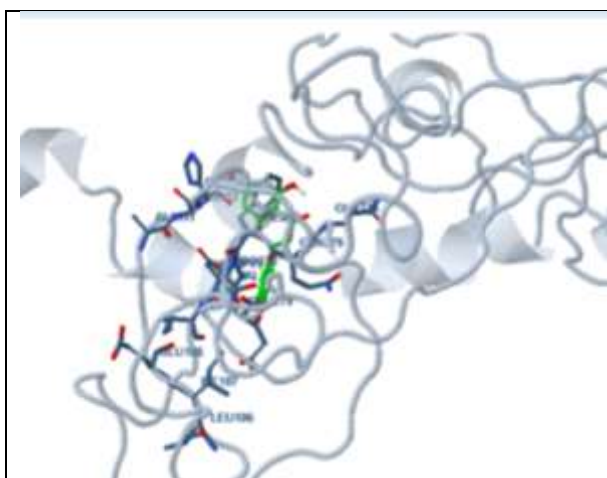
Linalool docking interacting amino acids



Linalyl acetate docking

Interaction Table		
polar	hydrophobic	other
O1 () - ASP100 [14] - O21	O8 () - LEU107 [14] - O21	C1 () - ASP100 [14] - O21
	O5 () - LEU107 [14] - O21	O5 () - GLN105 [14] - O21 - O21 - O21
	O8 () - LEU107 [14] - O21	C7 () - GLN105 [14] - O21
	O10 () - PHE177 [14] - O21	C16 () - GLN105 [14] - O21 - O21
	O2 () - PRO176 [14] - O2 - O21	
	O5 () - PRO176 [14] - O21	
	O2 () - PRO176 [14] - O2 - O21	
	O5 () - PRO176 [14] - O21	
	O2 () - PRO176 [14] - O2 - O21	
	O5 () - PRO176 [14] - O21	
	O8 () - PRO176 [14] - O21	

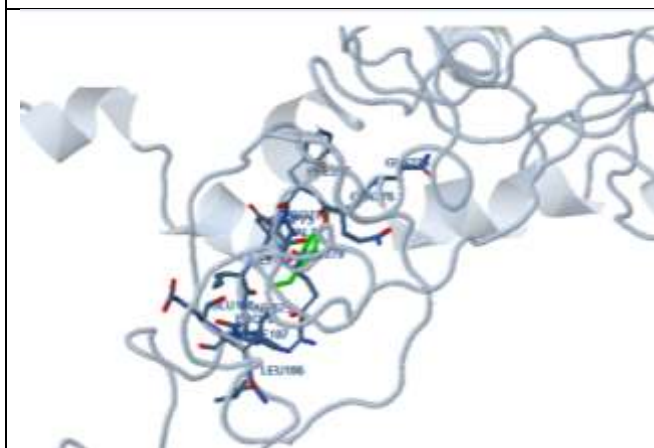
Linalyl acetate docking interacting amino acids



Interaction Table			
polar	hydrophobic	pi-pi	ether
OS (1) - ASP73 (14)	CA (1) - PRO278 (14)	CT (1) - PHE277 (14)	CR (1) - ASP73 (14)
HR (1) - ASP73 (14)	C14 (1) - PRO278 (14)	C2 (1) - PHE277 (14)	C13 (1) - ASP73 (14)
OA (1) - HR70 (14)	C13 (1) - PRO278 (14)	CR (1) - PHE277 (14)	OA (1) - HR70 (14)
	C15 (1) - PRO278 (14)	CR (1) - PHE277 (14)	C14 (1) - GLN276 (14)
		CT (1) - PHE277 (14)	CO (1) - GLN276 (14)
			OT (1) - PHE277 (14)
			OT (1) - PRO278 (14)
			OR (1) - GLU279 (14)

Luteolin docking

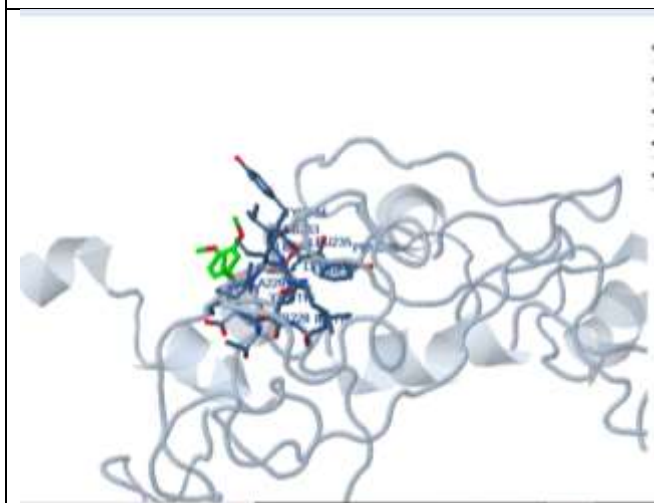
Luteolin docking interacting amino acids



Interaction Table	
hydrophobic	ether
C13 (1) - LEU74 (14)	C2 (1) - ASP73 (14)
CR (1) - LEU77 (14)	CR (1) - ASP73 (14)
C13 (1) - LEU77 (14)	C2 (1) - ARG75 (14)
CR (1) - PRO278 (14)	CT (1) - GLN276 (14)
CR (1) - PRO278 (14)	OT (1) - GLN276 (14)
CA (1) - PRO278 (14)	OT (1) - PRO278 (14)
CT (1) - PRO278 (14)	
C13 (1) - PRO278 (14)	

Methylchavicol docking

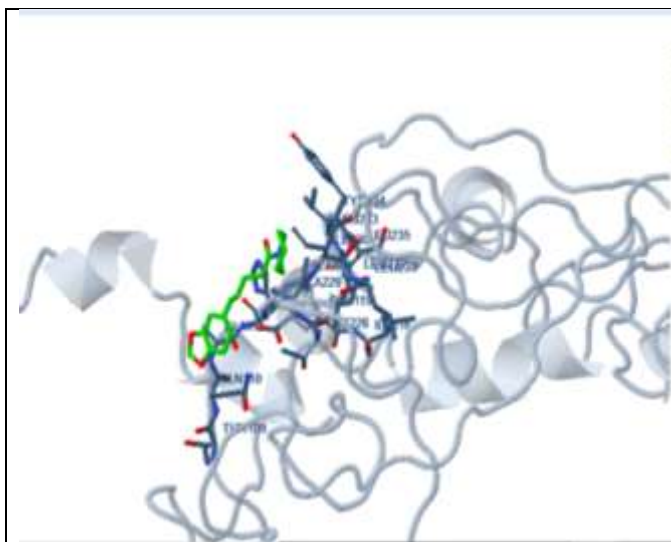
Methylchavicol docking interacting amino acids



Interaction Table	
hydrophobic	ether
CR (1) - ALA114 (14)	CT (1) - GLU115 (14)
CR (1) - ALA114 (14)	C13 (1) - GLU115 (14)
C13 (1) - LEU223 (14)	CR (1) - ALA229 (14)
CR (1) - LEU223 (14)	OT (1) - LEU223 (14)
CR (1) - LEU223 (14)	
CR (1) - PHE224 (14)	

Methyleugenol docking

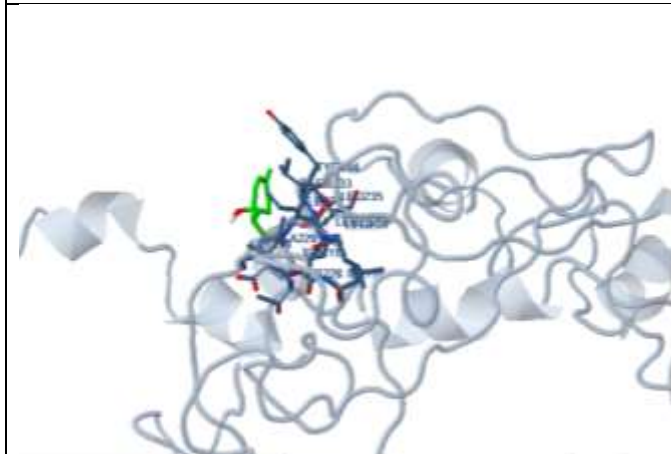
Methyleugenol docking interacting amino acids



Interaction Table							
hydrogen bonds		piH		hydrophobic		ether	
M1)	ALA14	O1)	GLN10	O2)	LEU20	O7)	GLN15
D1)	H	D4)	H	D6)	H	D14)	H
				O7)	LEU20	O8)	GLN15
				D7)	H	D8)	GLN15
						O11)	GLN15
						D4)	H
						O16)	GLN15
						D4)	H
						O18)	GLN15
						D4)	H
						O19)	GLN15
						D4)	H
						O21)	GLN15
						D4)	H
						O23)	GLN15
						D4)	H
						O24)	GLN15
						D4)	H
						O25)	GLN15
						D4)	H

Piperin docking

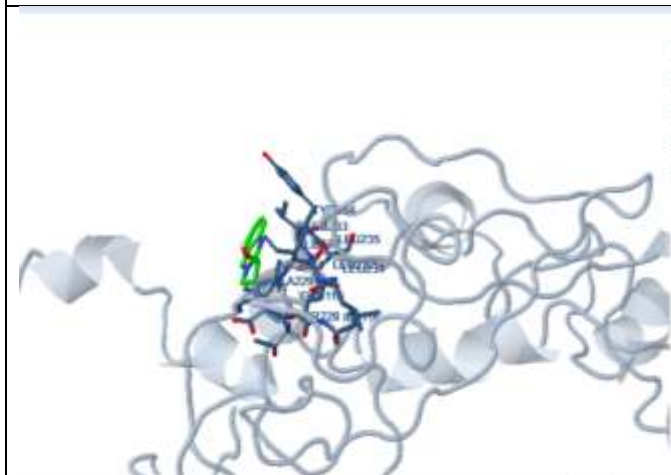
Piperin docking interacting amino acids



Interaction Table			
hydrophobic		ether	
O5)	ALA14	O9)	GLN15
D4)	H	D4)	H
O9)	ALA20		
D4)	H		
O9)	LEU20		
D4)	H		
O4)	LEU20		
D4)	H		
O7)	LEU20		
D4)	H		
O16)	THR24		
D4)	H		

Terpinen-4-ol docking

Terpinen-4-ol docking interacting of amino acids



Interaction Table						
hydrophobic		piH		ether		
O1)	ALA14	O3)	THR24	M1)	GLN15	
D4)	H	D4)	H	D11)	H	
O8)	ALA14			O7)	GLN15	
D4)	H			D4)	H	
O6)	ALA14			O5)	GLN15	
D4)	H			D4)	H	
O2)	ALA20			O1)	ALA20	
D4)	H			D11)	H	
				N1)	LEU20	
				D4)	H	
				H1)	LEU20	
				D11)	H	

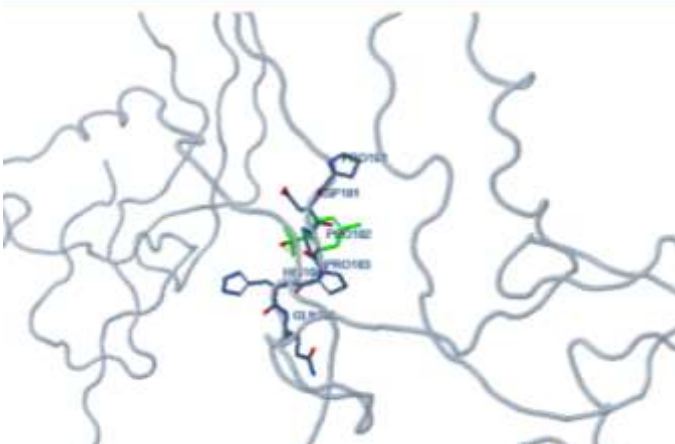
Vasicine docking

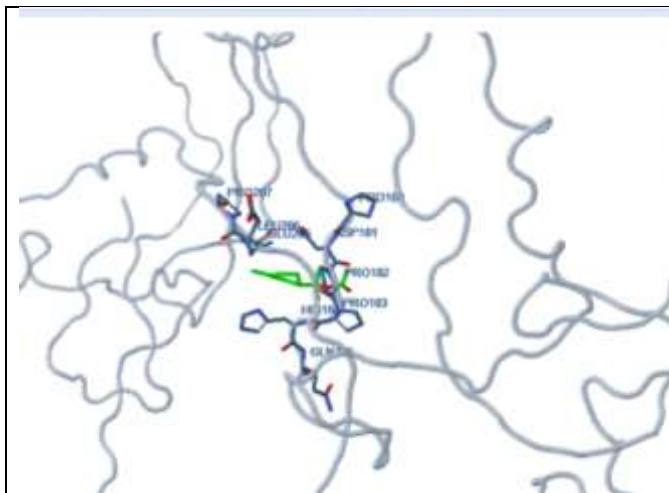
Vasicine docking interacting of amino acids

Table 6(a): Docking studies of NRAMP1

Phyto-compound	Docking score	No. of interactions	Docking (yes/no)
Alpha-terpineol	-3.64kcal/mol	9	Yes
Alpha-terpinyl acetate	-3.25kcal/mol	11	Yes
Ascorbic acid	-1.51kcal/mol	9	Yes
Bita-pinen	-3.01kcal/mol	15	Yes
Carvacrol	-3.12kcal/mol	16	Yes
Caryophyllene oxide	-3.83kcal/mol	10	Yes
Eugenol	-2.96kcal/mol	9	Yes
Fisetin	-3.73kcal/mol	21	Yes
Kaempferol	-3.64kcal/mol	16	Yes
Linalool	-2.98kcal/mol	13	Yes
Luteolin	-2.77kcal/mol	12	Yes
Linalyl acetate	-3.67kcal/mol	21	Yes
Methylchavicol	-3.21kcal/mol	10	Yes
Methyleugenol	-3.52kcal/mol	9	Yes
Piperine	-4.16kcal/mol	17	Yes
Terpinen-4-ol	-3.09kcal/mol	13	Yes
Vasicine	-3.07kcal/mol	10	Yes

Table 6(b): Docking images and their interacted amino acid residues.

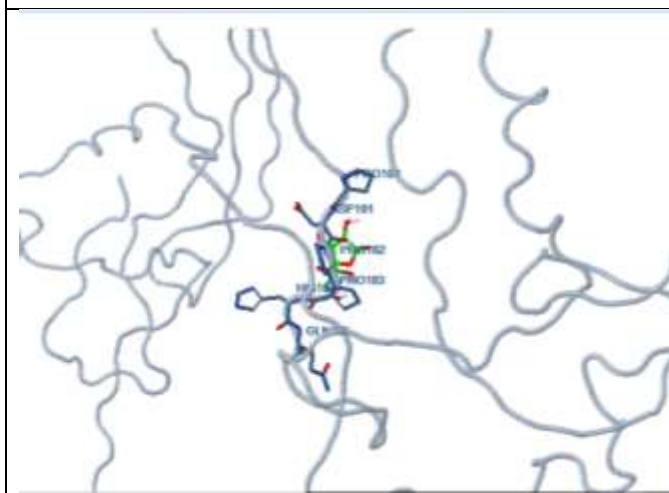
	<table border="1"> <thead> <tr> <th colspan="3">Interacted Residues</th> </tr> <tr> <th>hydrophobic</th> <th>cationic</th> <th>other</th> </tr> </thead> <tbody> <tr> <td>G235 - ASP36 D184 - SER</td> <td>H110 - ASP36 D184 - SER</td> <td>E132 - ASP36 D184 - SER G235 - ASP36 D184 - SER C736 - ASP36 D174 - SER D171 - ASP36 D170 - SER H110 - ASP36 D171 - SER G235 - ASP36 D184 - SER D711 - ASP36 D184 - SER</td> </tr> </tbody> </table>	Interacted Residues			hydrophobic	cationic	other	G235 - ASP36 D184 - SER	H110 - ASP36 D184 - SER	E132 - ASP36 D184 - SER G235 - ASP36 D184 - SER C736 - ASP36 D174 - SER D171 - ASP36 D170 - SER H110 - ASP36 D171 - SER G235 - ASP36 D184 - SER D711 - ASP36 D184 - SER
Interacted Residues										
hydrophobic	cationic	other								
G235 - ASP36 D184 - SER	H110 - ASP36 D184 - SER	E132 - ASP36 D184 - SER G235 - ASP36 D184 - SER C736 - ASP36 D174 - SER D171 - ASP36 D170 - SER H110 - ASP36 D171 - SER G235 - ASP36 D184 - SER D711 - ASP36 D184 - SER								
Alpha-terpineol docking	Alpha-terpineol docking interacting of amino acids									



Alpha-terpinyl acetate docking

Hydrophobic		Other	
O10 - HB34	[H] - 08	O10 - ASP181	[H] - 08
O10 - HB34	[H] - 08	O10 - ASP181	[H] - 08
O10 - HB34	[H] - 08	O10 - HB34	[H] - 08
O10 - HB34	[H] - 08	O10 - HB34	[H] - 08
O10 - HB34	[H] - 08	O10 - HB34	[H] - 08
O10 - HB34	[H] - 08	O10 - HB34	[H] - 08
O10 - HB34	[H] - 08	O10 - HB34	[H] - 08

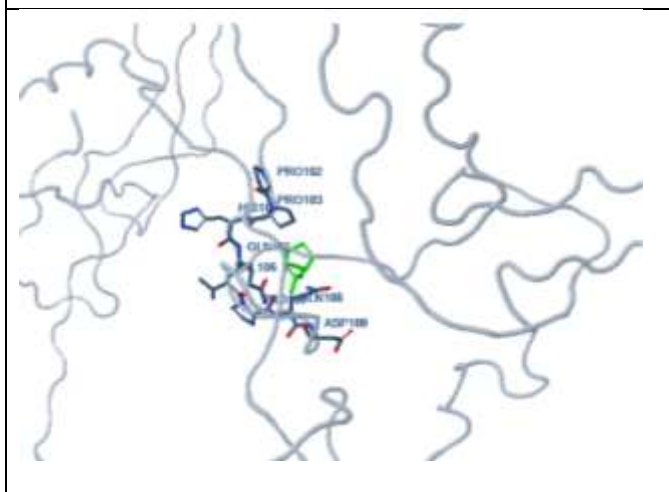
Alpha-terpinyl acetate docking interacting of amino acids



Ascorbic acid docking

Hydrophobic		Other	
O10 - ASP181	[H] - 08	O10 - ASP181	[H] - 08
H10 - ASP181	[H] - 08	O10 - ASP181	[H] - 08
		O10 - ASP181	[H] - 08
		H10 - ASP181	[H] - 08
		O10 - ASP181	[H] - 08
		H10 - PRO182	[H] - 08
		O10 - PRO182	[H] - 08

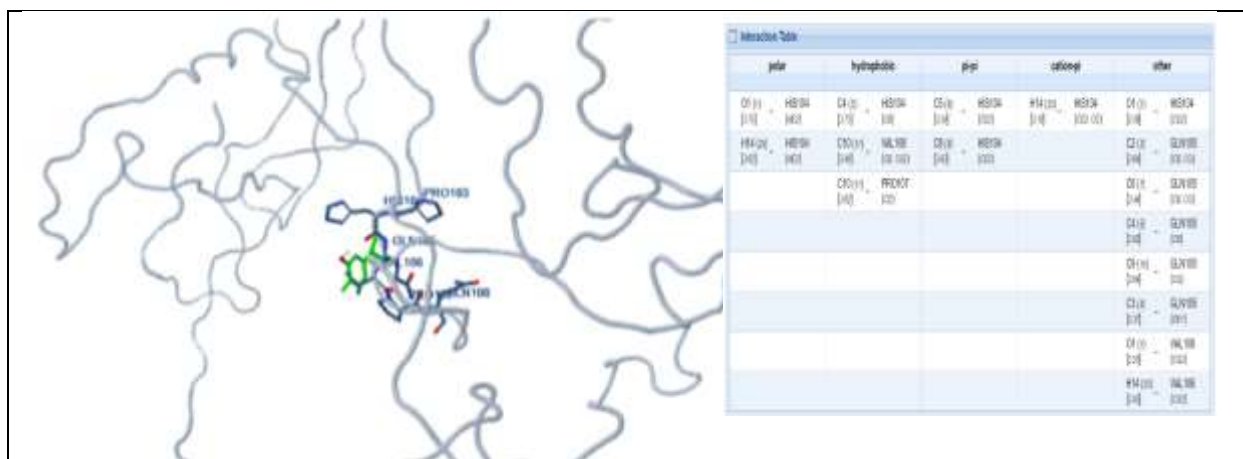
Ascorbic acid docking interact with amino acids



Beta-pinene docking

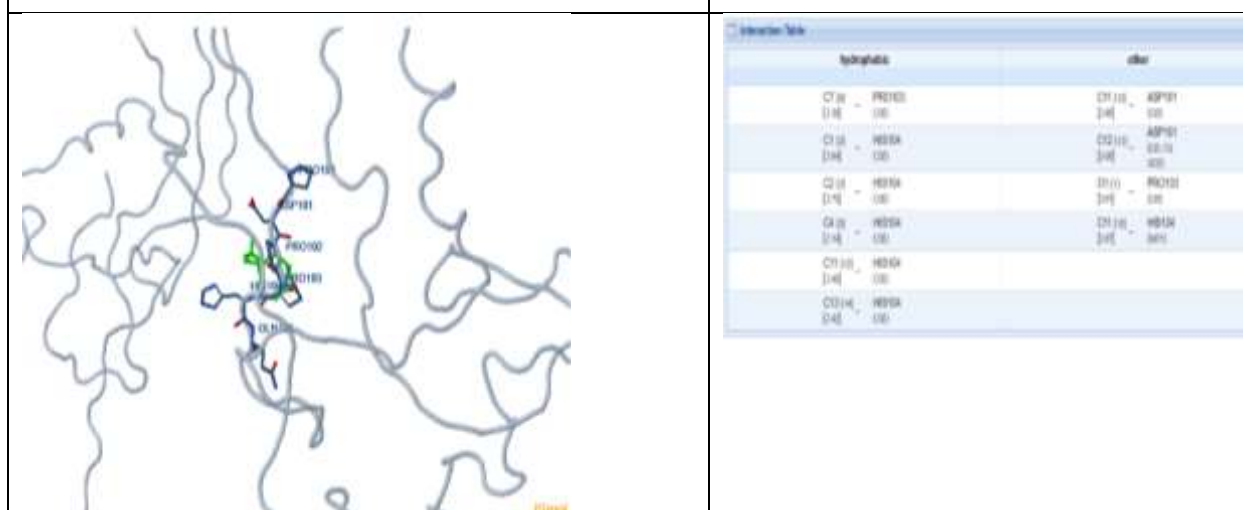
Hydrophobic		Other	
O10 - RX32	[H] - 08	O10 - ASP181	[H] - 08
O10 - RX32	[H] - 08	O10 - ASP181	[H] - 08
O10 - RX32	[H] - 08	O10 - ASP181	[H] - 08
O10 - RX32	[H] - 08	O10 - ASP181	[H] - 08
O10 - RX32	[H] - 08	O10 - ASP181	[H] - 08
O10 - RX32	[H] - 08	O10 - ASP181	[H] - 08
O10 - RX32	[H] - 08	O10 - ASP181	[H] - 08
O10 - RX32	[H] - 08	O10 - ASP181	[H] - 08
O10 - RX32	[H] - 08	O10 - ASP181	[H] - 08
O10 - RX32	[H] - 08	O10 - ASP181	[H] - 08

Beta-pinene docking interacting of amino acids



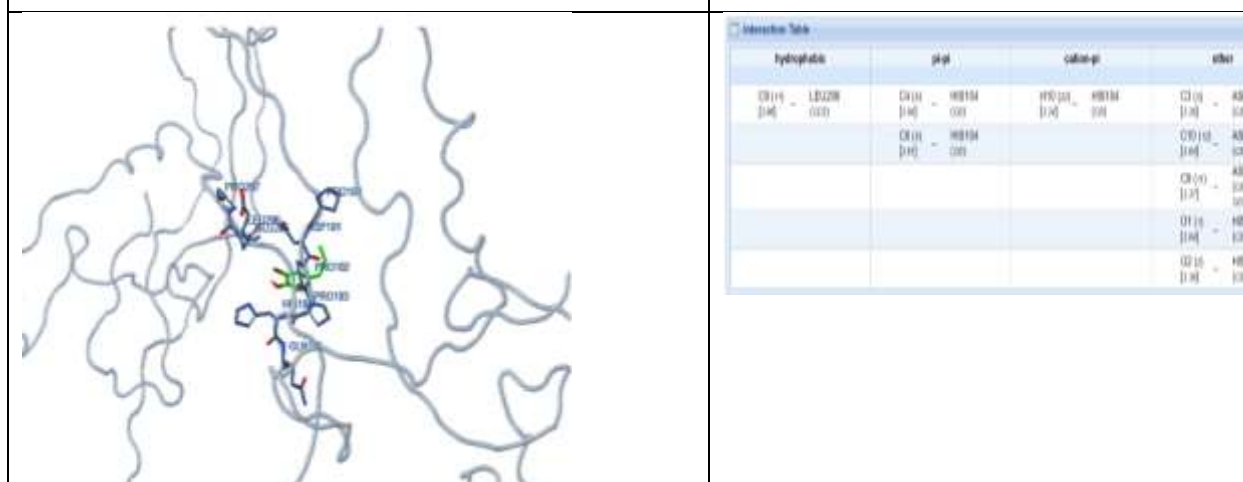
Carvacrol docking

Carvacrol docking interacting of amino acids



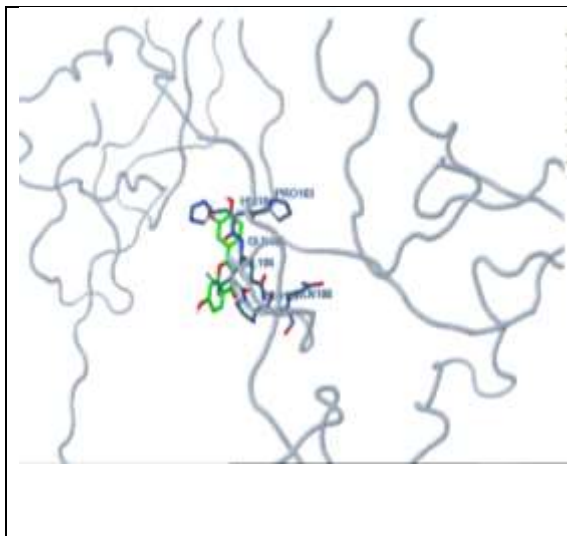
Caryophyllene oxide docking

Caryophyllene oxide docking interacting of amino acids



Eugenol docking

Eugenol docking interacting of amino acids



Interaction Table			
polar	hydrophobic	p-p	other
O2 (1) - GLN105 [2.4] - (24)	O2 (4) - PRO167 [2.4] - (24)	C15 (1) - HIS164 [2.4] - (24)	O6 (1) - HIS164 [2.4] - (24)
H7 (1) - GLN105 [2.4] - (24)	C11 (1) - PRO167 [2.4] - (24)	C4 (1) - HIS164 [2.4] - (24)	O1 (1) - GLN105 [2.4] - (24)
	C12 (1) - PRO167 [2.4] - (24)	C4 (1) - HIS164 [2.4] - (24)	C1 (7) - GLN105 [2.4] - (24)
	C7 (1) - PRO167 [2.4] - (24)	C15 (1) - HIS164 [2.4] - (24)	C18 (1) - GLN105 [2.4] - (24)
			C2 (1) - GLN105 [2.4] - (24)
			C3 (1) - GLN105 [2.4] - (24)
			C5 (1) - GLN105 [2.4] - (24)
			O8 (1) - GLN105 [2.4] - (24)
			O3 (1) - GLN105 [2.4] - (24)
			O4 (1) - VAL108 [2.4] - (24)
			O4 (1) - PRO167 [2.4] - (24)

Fisetin docking

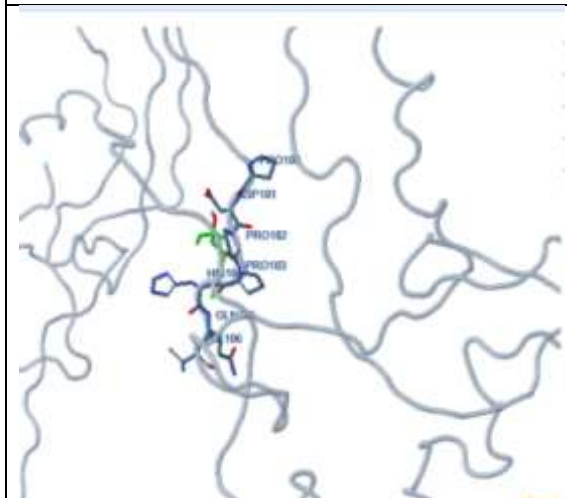
Fisetin docking interacting of amino acids



Interaction Table		
polar	p-p	other
O6 (1) - ASP101 [2.4] - (24)	C2 (1) - HIS164 [2.4] - (24)	H9 (1) - ASP101 [2.4] - (24)
H9 (1) - ASP101 [2.4] - (24)	C3 (1) - HIS164 [2.4] - (24)	C15 (1) - ASP101 [2.4] - (24)
O3 (1) - GLN105 [2.4] - (24)	O8 (1) - HIS164 [2.4] - (24)	C14 (1) - ASP101 [2.4] - (24)
	C2 (1) - HIS164 [2.4] - (24)	O4 (1) - PRO167 [2.4] - (24)
		H7 (1) - PRO167 [2.4] - (24)
		O1 (1) - HIS164 [2.4] - (24)
		C7 (1) - GLN105 [2.4] - (24)
		C18 (1) - GLN105 [2.4] - (24)
		O5 (1) - GLN105 [2.4] - (24)

Kaempferol docking

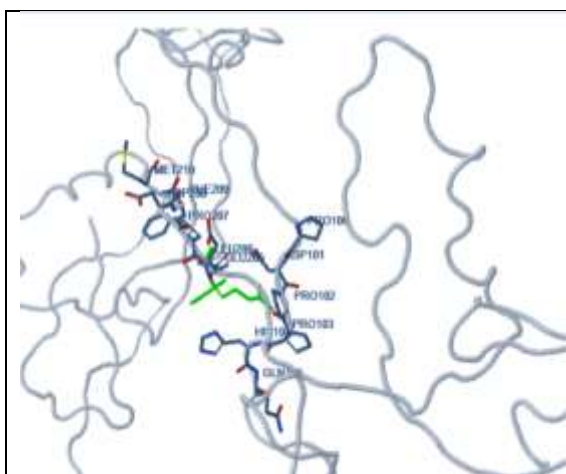
Kaempferol docking interacting of amino acids



Interaction Table		
polar	hydrophobic	other
O1 (1) - ASP101 [2.4] - (24)	C8 (1) - HIS164 [2.4] - (24)	C1 (1) - ASP101 [2.4] - (24)
H15 (1) - ASP101 [2.4] - (24)	C7 (1) - HIS164 [2.4] - (24)	C4 (1) - ASP101 [2.4] - (24)
	C8 (1) - HIS164 [2.4] - (24)	O1 (1) - ASP101 [2.4] - (24)
	C18 (1) - HIS164 [2.4] - (24)	H9 (1) - ASP101 [2.4] - (24)
		C5 (1) - ASP101 [2.4] - (24)
		C13 (1) - ASP101 [2.4] - (24)
		C18 (1) - HIS164 [2.4] - (24)

Linalool docking

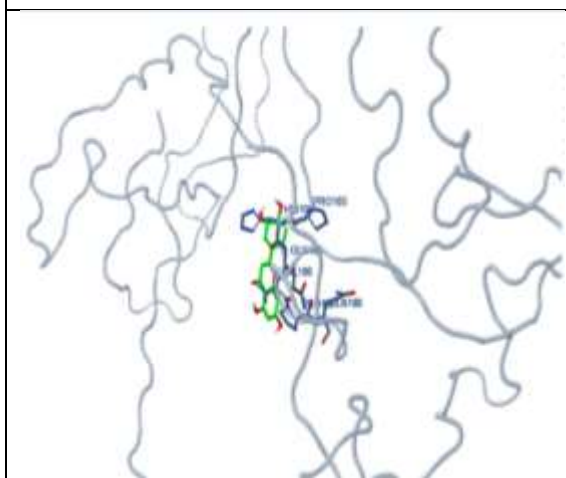
Linalool docking interacting of amino acids



Luteolin docking

hydrophobic		other	
O5 (H) - HE104 [14] - 101		O7 (H) - ASP101 [14] - 101	
O9 (H) - HE104 [14] - 101		O8 (H) - ASP101 [14] - 101	
O10 (H) - LE106 [14] - 102-103		O7 (H) - ASP101 [14] - 101	
O12 (H) - LE106 [14] - 101		O11 (H) - ASP101 [14] - 101	
O12 (H) - PRO102 [14] - 101		O2 (H) - HE104 [14] - 101	
		O8 (H) - HE104 [14] - 101	
		O1 (H) - LE106 [14] - 101-101	

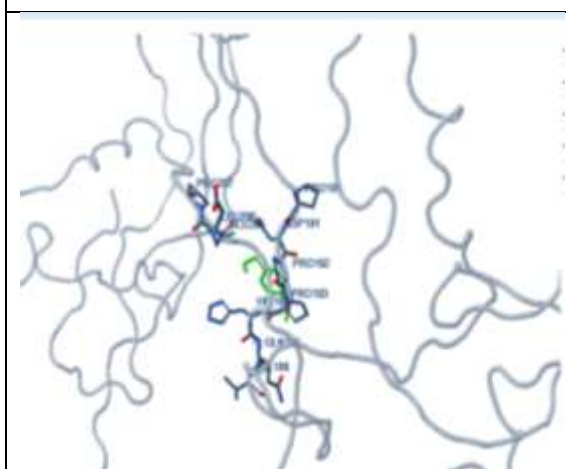
Luteolin docking interacting of amino acids



Linalyl acetate docking

polar	hydrophobic	p-p	other
O1 (H) - GLN105 [14] - 101	O7 (H) - PRO102 [14] - 102-103	O5 (H) - HE104 [14] - 101-102	O1 (H) - GLN105 [14] - 101-102
	O11 (H) - PRO102 [14] - 101	O8 (H) - HE104 [14] - 101-102	O2 (H) - GLN105 [14] - 101-102
		O10 (H) - HE104 [14] - 101-102	O3 (H) - GLN105 [14] - 101
		O9 (H) - HE104 [14] - 101	O10 (H) - GLN105 [14] - 101
		O6 (H) - HE104 [14] - 101	O7 (H) - GLN105 [14] - 101
		O12 (H) - HE104 [14] - 101	O8 (H) - GLN105 [14] - 101-102
		O4 (H) - HE104 [14] - 101	O9 (H) - GLN105 [14] - 101
			O2 (H) - VAL106 [14] - 101
			WT (H) - VAL106 [14] - 101
			O2 (H) - PRO102 [14] - 101
			WT (H) - PRO102 [14] - 101

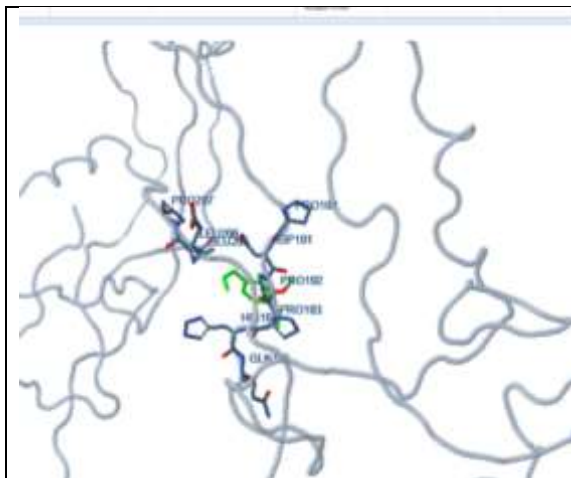
Linalyl acetate docking interacting of amino acids



Methylchavicol docking

hydrophobic	p-p	other
O5 (H) - PRO102 [14] - 101	O4 (H) - HE104 [14] - 101	O7 (H) - ASP101 [14] - 101
O9 (H) - HE104 [14] - 101	O11 (H) - HE104 [14] - 101	O2 (H) - ASP101 [14] - 101
O10 (H) - LE106 [14] - 101		O8 (H) - ASP101 [14] - 101
		O1 (H) - HE104 [14] - 101

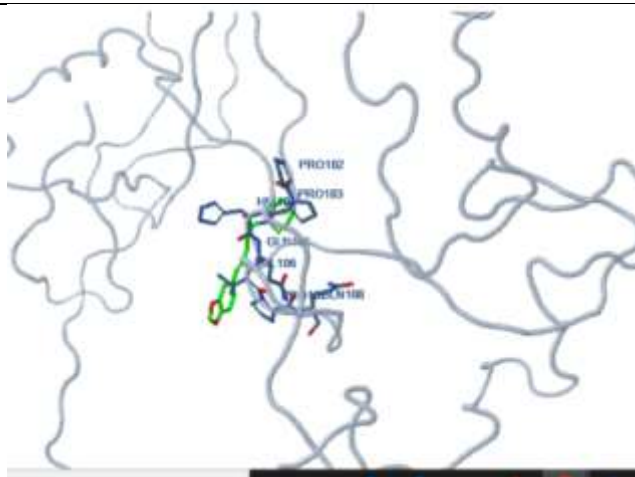
Methylchavicol docking interacting of amino acids



Methyleugenol docking

Hydrophobic			H-B			Other		
C6 (H)	PRO101	3.91	C5 (H)	ASP104	2.15	C1 (H)	ASP101	2.05
C7 (H)	ASP104	2.15				C5 (H)	ASP101	2.05
C8 (H)	GLN105	2.01				C2 (H)	ASP101	1.95
						C3 (H)	ASP101	1.95
						C4 (H)	ASP101	1.95
						C11 (H)	ASP101	1.95

Methyleugenol docking interacting of amino acids



Piperine docking

Hydrophobic			Other		
C1 (H)	PRO102	3.75	C11 (H)	ASP101	2.05
C2 (H)	PRO102	2.45	N6 (H)	ASP101	1.95
C3 (H)	ASP104	2.15	C5 (H)	ASP101	1.95
C4 (H)	ASP104	2.15	C6 (H)	ASP101	1.95
C7 (H)	PRO107	2.01	C7 (H)	ASP101	1.95
C8 (H)	PRO107	2.01	C8 (H)	ASP101	1.95
C9 (H)	PRO107	2.01	C9 (H)	ASP101	1.95
C10 (H)	PRO107	2.01	C10 (H)	ASP101	1.95
			C11 (H)	ASP101	1.95
			C12 (H)	ASP101	1.95
			C13 (H)	ASP101	1.95
			C14 (H)	ASP101	1.95

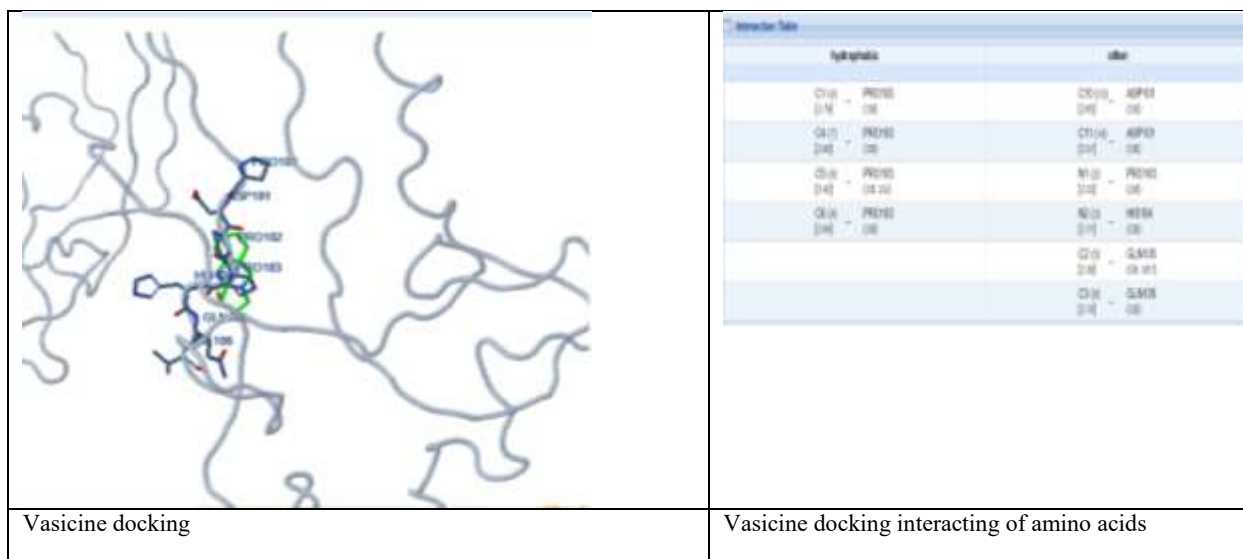
Piperine docking interacting of amino acids



Terpinen-4-ol docking

Hydrophobic			Other		
C1 (H)	ASP101	3.91	C5 (H)	ASP101	2.05
C2 (H)	ASP101	3.91	C6 (H)	ASP101	2.05
			C7 (H)	ASP101	2.05
			C8 (H)	ASP101	2.05
			C9 (H)	ASP101	2.05
			C10 (H)	ASP101	2.05
			C11 (H)	ASP101	2.05
			C12 (H)	ASP101	2.05

Terpinen-4-ol docking interacting of amino acids



4. Discussion

As per the docking results it is seen that Kaempferol docks with CCL2 with docking score of 4.67 with 19 interactions and NRAMP1 docks with Kaempferol with docking score of -3.64 with 16 interactions. CCL2 docks with Fisetin with docking score of -4.84 with 16 interactions and NRAMP1 docks with Fisetin with docking score of -3.73 with 21 interactions. CCL2 docks with Piperin with docking score of -5.04 with 16 interactions and NRAMP1 docks with Piperin with docking score of -4.16 with 17 interactions.

5. Conclusion

As per the results it is seen that phytochemicals Kaempferol, Fisetin and Piperin with docking score of -4.84 with 16 interactions. NRAMP1 docks with Fisetin with docking score of -3.73 with 21 interactions. CCL2 docks with Kaempferol with docking score -4.67 with 19 interactions. NRAMP1 docks with Kaempferol with docking score of -3.64 with 16 interactions.

Hence the above compound can be used as ligands for treating TUBERCULOSIS.

References

1. Bloom BR, Atun R, Cohen T, Dye C, Fraser H, Gomez GB, Knight G, Murray M, Nardell E, Rubin E, Salomon J, Vassall A, Volchenkov G, White R, Wilson D, Yadav P. Tuberculosis. In: Holmes KK, Bertozzi S, Bloom BR, Jha P, editors. Major Infectious Diseases. 3rd ed. Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2017 Nov 3. Chapter 11. PMID: 30212088.
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