ESTABLISHED IN-SILICO AYURVEDIC REMEDY FOR GERMAN MEASLES

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Abstract. German measles (also known as Rubella) a viral illness that causes a rash and fever; though mild and self-limiting but can be serious in pregnant women as it can cause birth defects in the developing fetus. Vaccination is the most effective way to prevent rubella. It usually starts on the face and spreads to the rest of the body. The rash is sometimes itchy and is not as bright as that of measle. Rubella is usually spread from one person to the next through the air via coughs of people who are infected. People are infectious during the week before and after the appearance of the rash. Babies with CRS may spread the virus for more than a year. Only humans are infected Insects do not spread the disease. The name "rubella" is from Latin and means little red. It was first described as a separate disease by German physicians in 1814 resulting in the name "German measles".The FASTA sequence is retrieved from Genbank database. 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, Fumaria parviflora, Tinospora cordifolia, Azadirachta indica, Picrohiza kurroa 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 violations was considered for further docking studies.

The phytocompounds palmatine, syringin, cryptopine with docking score of -4.33 kcal/mol with 25 interactions. Cdk docks with cryptopine with docking score of 6.08 kcal/mol with 29 interactions.

MON1B docks with berberine with docking score of 5.03 kcal/mol with 21 interactions. Cds docks with bernerin with docking score of -9.1kcal/mol with 33 interactions.

Keywords: German Measles, Rubella, Bioinformatics, Docking, Phytocompound.

1 Introduction

German measles, a viral illness, causes a rash and fever. The rash is sometimes itchy and is not as bright as that of measles. Swollen lymph nodes are common and may last a few weeks [1]. Associated complications are bleeding problems, and inflammation of nerves. Early pregnancy infection usually may results in a miscarriage or sometime a congenital rubella syndrome (CRS) child. Alongside symptoms of CRS manifest as problems with the eyes such as cataracts, deafness, as well as affecting the heart and brain can also be seen [2]. Problems are rare after the 20th week of pregnancy. Rubella is usually spread from one person to the next through the air via coughs of people who are infected. People are infectious during the week before and after the

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appearance of the rash [3]. Babies with CRS may spread the virus for more than a year. Only humans are infected Insects do not spread the disease. Once recovered, people are immune to future infections [4]. Testing is available that can verify immunity. Diagnosis is confirmed by finding the virus in the blood, throat, or urine. Testing the blood for antibodies may also be useful [5]. Rubella is preventable with the rubella vaccine with a single dose being more than 95% effective. Often it is given in combination with the measles vaccine and mumps vaccine, known as the MMR vaccine [6].

Genes involved:-

CDK8 : Cyclin dependent kinase 8 (CDK8) is a serine/threonine kinase that belongs to the family of Cyclin-dependent kinases (CDKs), which require the association of their cyclin partners to be active [7].

MON1B : (MON1 Homolog B, Secretory Trafficking Associated) is a Protein Coding gene. [8].

2. Materials and Methodology

The FASTA sequence of the gene receptors were retrieved from Genbank. Their 3d Structure was modelled using modeller. Phytocompounds as SMILES from medicinal plants Ocimum sanctum, Fumaria parviflora, Tinospora cordifolia, Azadirachta indica, Picrohiza kurroa are retrieved from PubChem and using the Lipinski's rule of five the compounds' drug-likeliness is checked using molinspiration software. Finally docking of the selected phytocompounds are done with the best model generated by modeler [9].

Gene receptor	Genbank accession number	Homologous templates
CDK8	AHB86974.1	8AD1
MON1B	NP_055755.1	7qlaA 5lddA 7zu0F

Table 1: Accession number of the gene receptor with their homologous templates.

3. Results

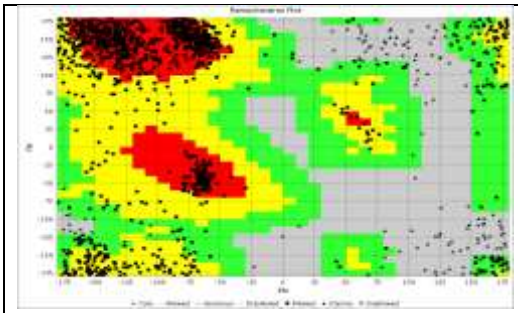
The modeler generated modes are verified using Ramachandran plot (Hollingsworth and Karplus, 2010) server (Table 2 and Fig. 1).

Table 2(a): Ramachandran plot analysis of CDK8

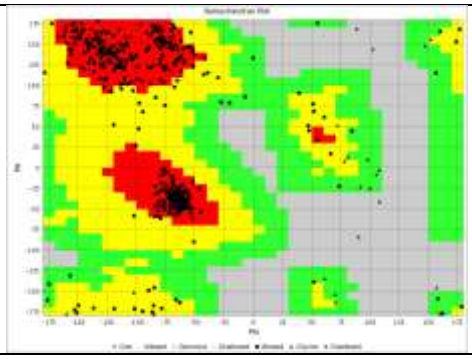
	# res in phipsi cor e	# res in phipsi allowed	# res in phipsi generous	# res in phipsi outside	
Model1	796 (60%)	297 (22%)	125 (9%)	100 (7%)	selected
Model2	748 (56%)	302 (22%)	137 (10%)	131 (9%)	
Model3	677 (51%)	329 (24%)	170 (12%)	142 (10%)	
Model4	760 (57%)	290 (22%)	130 (9%)	138 (10%)	
Model5	755 (57%)	311 (23%)	143 (10%)	109 (8%)	

Table 2(b): Ramachandran plot analysis of MON1B

	# res in phipsi core	# res in phipsi allowed	# res in phipsi generous	# res in phipsi outside	
Model1	475 (86%)	53 (9%)	13 (2%)	6 (1%)	
Model2	480 (87%)	52 (9%)	11 (2%)	4 (0%)	
Model3	480 (87%)	50 (9%)	11 (2%)	6 (1%)	
Model4	482 (88%)	51 (9%)	11 (2%)	3 (0%)	
Model5	484 (88%)	45 (8%)	16 (2%)	2 (0%)	selected



CDK8



MON1B

Fig. 1: Ramachandran Plot of the best model

The medicinal plants, Ocimum sanctum, Fumaria parviflora, Tinospora cordifolia, Azadirachta indica, Picrohiza kurroa (Table 3).

Table 3: Phytocomponds and their SMILES from Pubchem

Plant : *Ocimum sanctum*	
Phytocompound	**SMILES**
Ursolic Acid	C[C@@H]1CC[C@@]2(CC[C@@]3(C(=CC[C@H]4[C@]3(CC[C@@H]5[C@@]4(CC[C@@H](C5(C)C)O)C)C)[C@@H]2[C@H]1C)C)C(=O)O
Oleanic Acid	C[C@]12CC[C@@H](C([C@@H]1CC[C@@]3([C@@H]2CC=C4[C@]3(CC[C@@]5([C@H]4CC(CC5)(C)C)C(=O)O)C)C)(C)C)O
Rosmarinic	C1=CC(=C(C=C1C[C@H](C(=O)O)OC(=O)/C=C/C2=CC(=C(C=C2)O)O)O)O
Eugenol	COC1=C(C=CC(=C1)CC=C)O
Carvacol	CC1=C(C=C(C=C1)C(C)C)O

Plant : *Fumaria parviflora*	
Phytocompound	**SMILES**
Triterpenoid	C[C@]12CC[C@@H]([C@@]([C@@H]1CC[C@@]3([C@@H]2CC=C4[C@]3(CC[C@@]5([C@H]4CC(CC5)(C)C)C(=O)O)C)C)(C)COS(=O)(=O)O)O
Fumaricine	CN1CCC2=CC(=C(C=C2[C@@]13CC4=C([C@@H]3O)C5=C(C=C4)OCO5)OC)OC
Cryptopine	CN1CCC2=CC(=C(C=C2C(=O)CC3=C(C1)C4=C(C=C3)OCO4)OC)OC
Adlumine	CN1CCC2=CC(=C(C=C2[C@H]1[C@@H]3C4=C(C5=C(C=C4)OCO5)C(=O)O3)OC)OC
Bicuculline	CN1CCC2=CC3=C(C=C2[C@H]1[C@H]4C5=C(C6=C(C=C5)OCO6)C(=O)O4)OCO3

Plant *: Azadirachta indica*	
Phytocompound	**SMILES**
Limonoic acid	C[C@]1(CC[C@H]2[C@]([C@@]13[C@H](O3)C(=O)O)(C(=O)C[C@@H]4[C@@]2([C@@H](OC4(C)C)CC(=O)O)CO)C)[C@H](C5=COC=C5)O
Glycerides	CCCCCCCCCCCCC(=O)OCC(CO)O
Polyphenol	C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C(=C3)O)O)O)OC(=O)C4=CC(=C(C(=C4)O)O)O
Beta-sitosterol	CC[C@H](CC[C@@H](C)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C)C(C)C
Quercetin	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O

Plant : *Tinospora cordifolia*	
Phytocompounds	**SMILES**
Tinosporide	C[C@@]12CC[C@@H]3C(=O)O[C@H](C[C@]3([C@@H]1[C@H]4[C@H]5[C@@H]([C@@]2(C(=O)O4)O)O5)C)C6=COC=C6
Isocolumbin	C[C@@]12CC[C@@H]3C(=O)O[C@@H](C[C@]3([C@@H]1[C@@H]4C=C[C@]2(C(=O)O4)O)C)C5=COC=C5
Palmatine	COC1=C(C2=C[N+]3=C(C=C2C=C1)C4=CC(=C(C=C4CC3)OC)OC)OC
Berberine	COC1=C(C2=C[N+]3=C(C=C2C=C1)C4=CC5=C(C=C4CC3)OCO5)OC
Syringin	COC1=CC(=CC(=C1O[C@H]2[C@@H]([C@H]([C@@H]([C@H](O2)CO)O)O)O)OC)/C=C/CO

Plant : *Picrohiza kurroa*	
Phytocompounds	**SMILES**
Picroside	COC1=C(C=CC(=C1)C(=O)OC2C3C=COC(C3C4(C2O4)CO)O[C@H]5[C@@H]([C@H]([C@@H]([C@H](O5)CO)O)O)O)O
-mannitol D	C([C@H]([C@H]([C@@H]([C@@H](CO)O)O)O)O)O
Apocynin	CC(=O)C1=CC(=C(C=C1)O)OC
Catalpol	C1=CO[C@H]([C@H]2[C@@H]1[C@@H]([C@H]3[C@@]2(O3)CO)O)O[C@H]4[C@@H]([C@H]([C@@H]([C@H](O4)CO)O)O)O
Veronicoside	C1=CC=C(C=C1)C(=O)O[C@H]2[C@@H]3C=CO[C@H]([C@@H]3[C@@]4([C@H]2O4)CO)O[C@H]5[C@@H]([C@H]([C@@H]([C@H](O5)CO)O)O)O

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

Plant *: Azadirachta indica*	
Phytocompound	**SMILES**
Limonoic acid	C[C@]1(CC[C@H]2[C@]([C@@]13[C@H](O3)C(=O)O)(C(=O)C[C@@H]4[C@@]2([C@@H](OC4(C)C)CC(=O)O)CO)C)[C@H](C5=COC=C5)O
Glycerides	CCCCCCCCCCCCC(=O)OCC(CO)O
Polyphenol	C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C(=C3)O)O)O)OC(=O)C4=CC(=C(C(=C4)O)O)O
Beta-sitosterol	CC[C@H](CC[C@@H](C)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C)C(C)C
Quercetin	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O

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

Phytocompounds	miLogP	TPSA	natoms	MW	nON	nOHNH	nrotb	volume	nviolations
Ursolic acid	6.79	57.53	33	456.71	3	2	1	471.49	1
Oleanic Acid	6.72	57.53	33	456.71	3	2	1	471.14	1
Rosmarinic	1.63	144.52	26	360.32	8	5	7	303.54	0
Eugenol	2.10	29.46	12	164.20	2	1	3	162.14	0
Carvacol	3.81	20.23	11	150.22	1	1	1	158.57	0
Limonoic acid	0.48	167.03	36	506.55	10	4	6	446.14	1
Glycerides	4.57	66.76	20	288.43	4	2	15	308.45	0
Polyphenol	2.25	197.36	33	458.38	11	8	4	367.57	2
Beta-sitosterol	8.62	20.23	30	414.72	1	1	6	456.52	1
Quercetin	1.63	131.35	22	302.24	7	5	1	240.08	0
Triterpenoid	3.22	121.13	38	552.77	7	3	4	519.81	1
Fumaricine	2.28	60.40	27	369.42	6	1	2	329.89	0
Cryptopine	2.50	57.24	27	369.42	6	0	2	335.17	0
Adlumine	2.63	66.48	28	383.40	7	0	3	333.36	0
Bicuculline	2.88	66.48	27	367.36	7	0	1	306.20	0
Picroside	-1.05	197.14	36	512.46	13	6	8	424.04	3
D-mannitol	-3.10	121.37	12	182.17	6	6	5	161.66	1

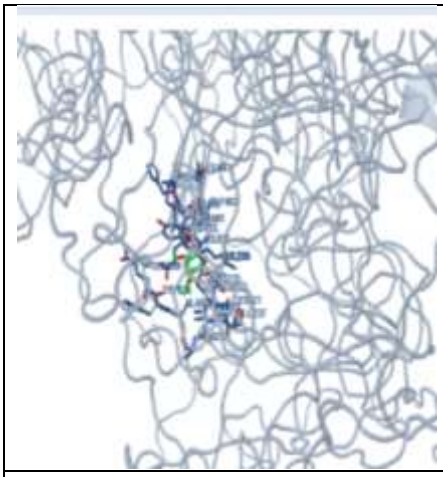
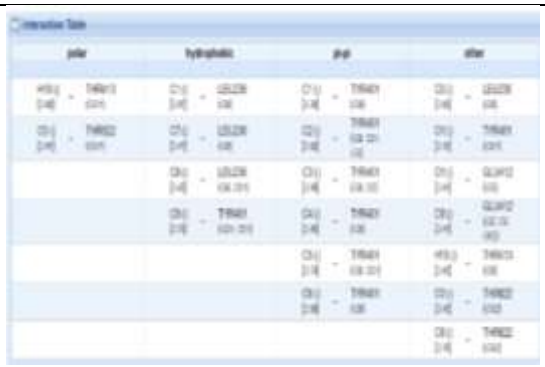
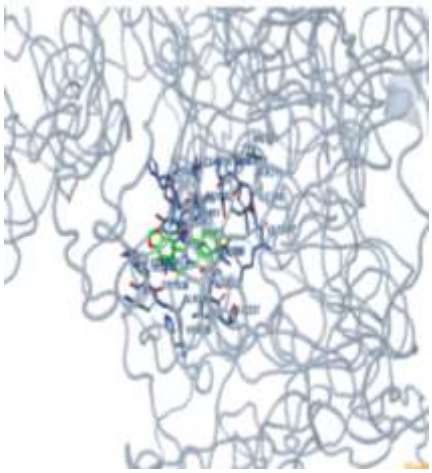
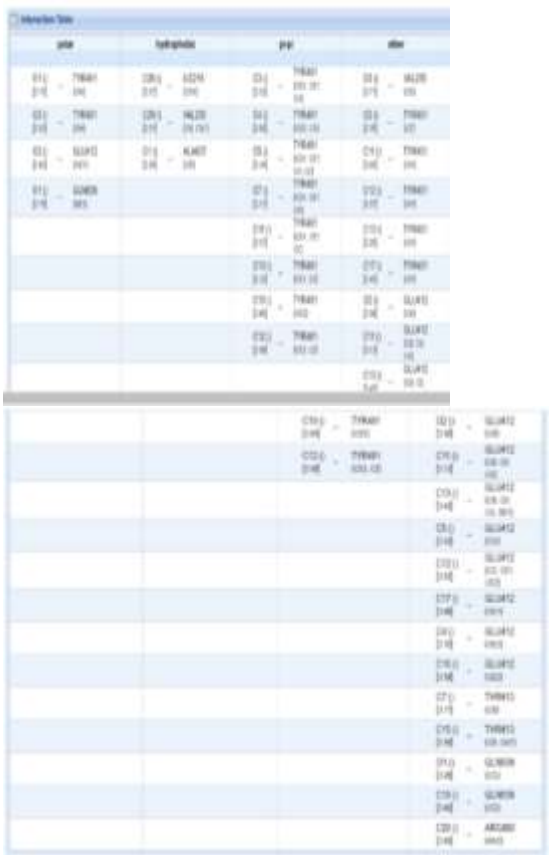
Apocynin	1.18	46.53	12	166.18	3	1	2	153.15	0
Catalpol	-2.81	161.60	25	362.33	10	6	4	299.11	1
Veronicoside	-0.39	167.68	33	466.44	11	5	7	390.47	1
Tinosporide	2.02	98.51	27	374.39	7	1	1	318.35	0
Isocolumbin	2.27	85.98	26	358.39	6	1	1	313.96	0
Palmatine	-0.05	40.82	26	352.41	5	0	4	323.46	0
Berberine	0.20	40.82	25	336.37	5	0	2	296.30	0
Syringin	-0.66	138.08	26	372.37	9	5	7	327.51	0

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

Table 5(a): Docking studies of CDK8

Phytocompound	Docking score	No.of interactions	Docking yes/no
apocynin	-4.74	19	yes
Berberin	-9.10	33	Yes
bicuculline	-5.90	17	yes
Carvacrol	-5.06	26	yes
Cryptopine	-06.08	29	yes
Eugenol	-4.88	14	yes
Fumaricine	-6.29	24	yes
Glycerides	-3.75	27	yes
Isocolumbin	-6.25	22	yes
Palmatine	-8.43	21	yes
Quercetin	-6.30	28	yes
Rosmarinic	-5.87	36	yes
Syringin	-4.54	27	yes
Tinosporide	-7.20	29	yes

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

	
Apocynin docking	Apocynin docking interacting of two amino acids
	
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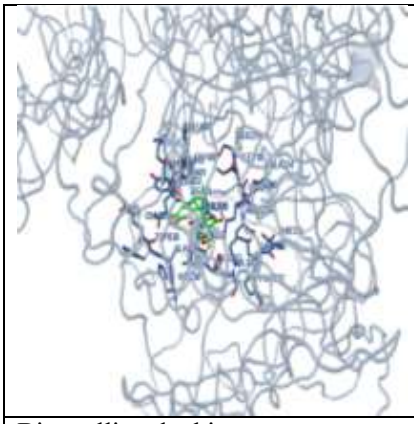	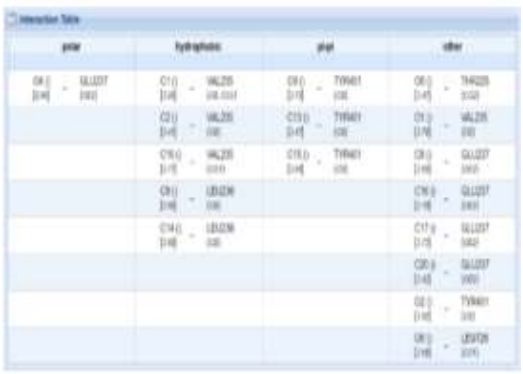
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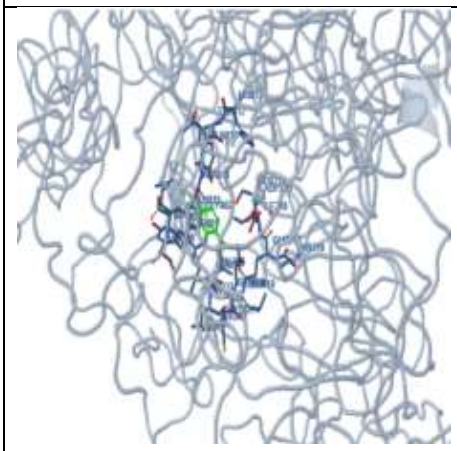	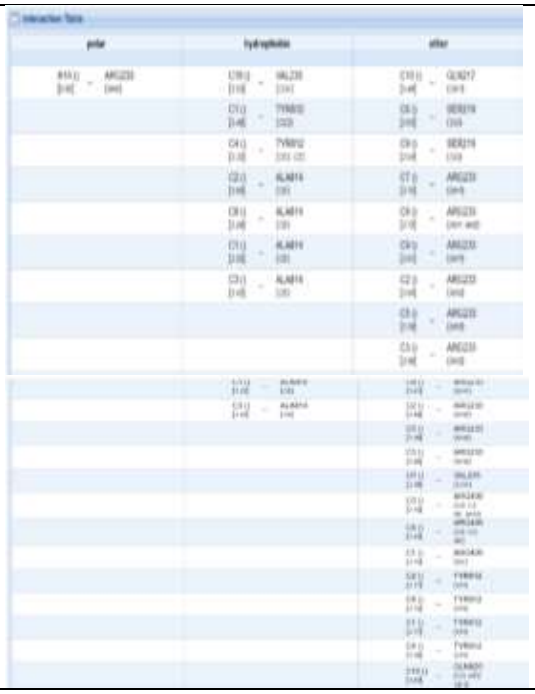
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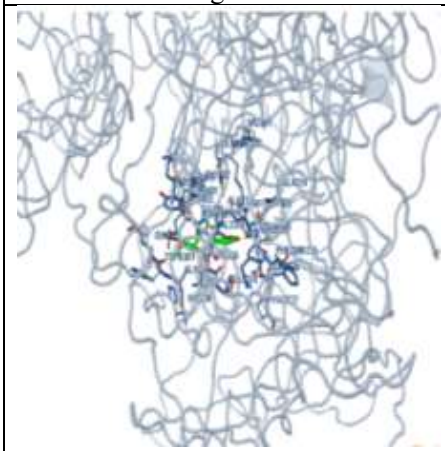	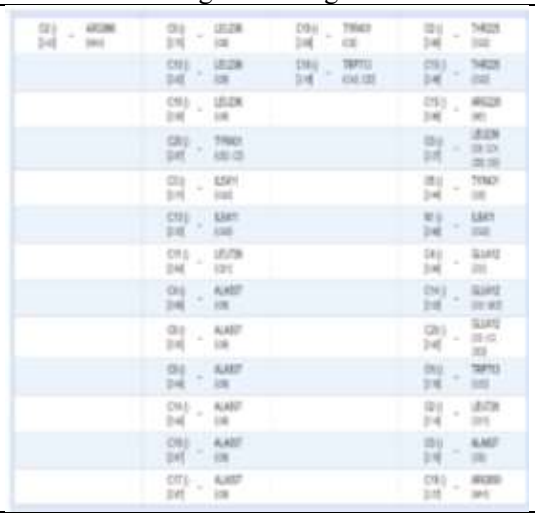
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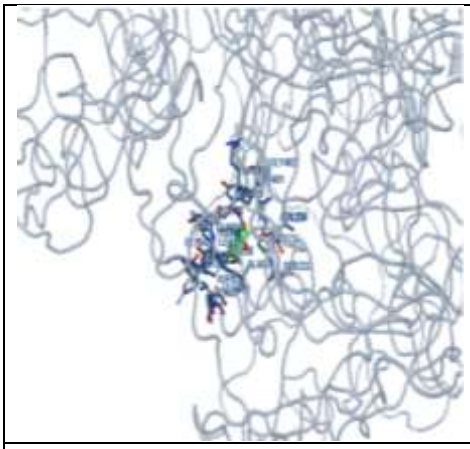	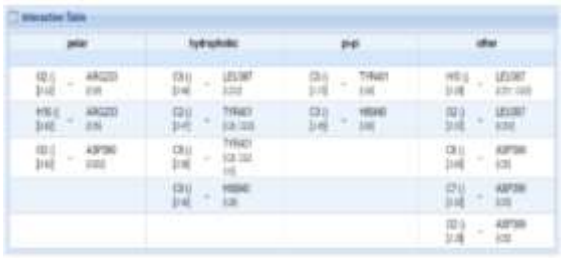
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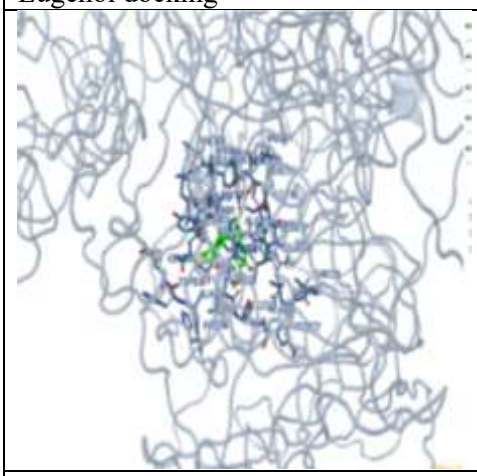
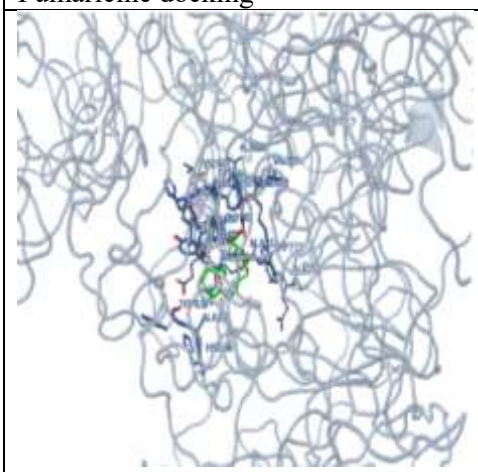
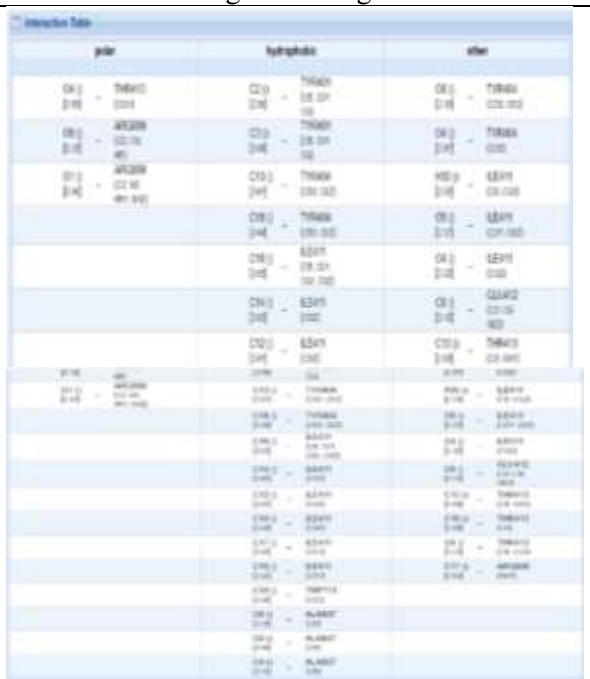
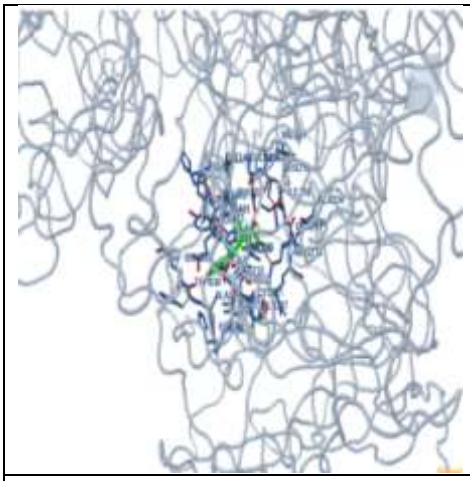
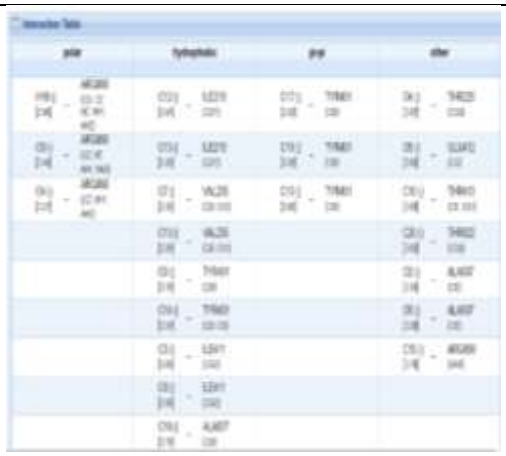
	
Fumaricine docking	Fumaricine docking interacting of two amino acids
	
Glycerides docking	Glycerides docking interacting of two amino acids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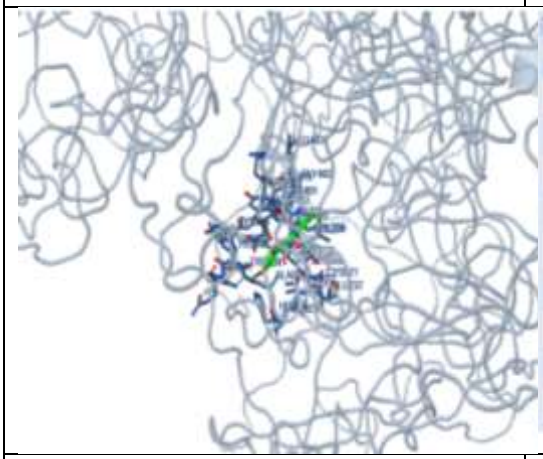	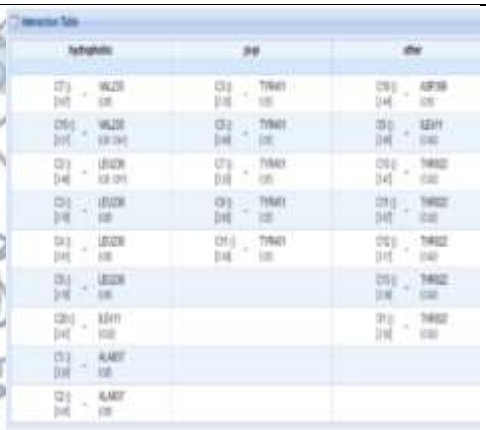
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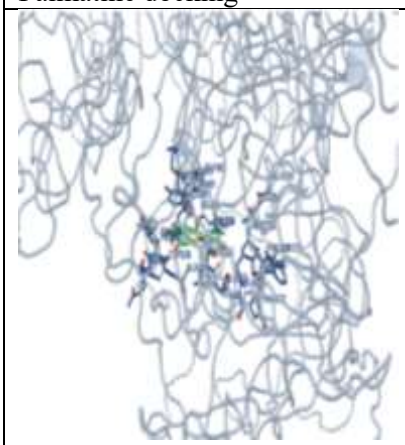
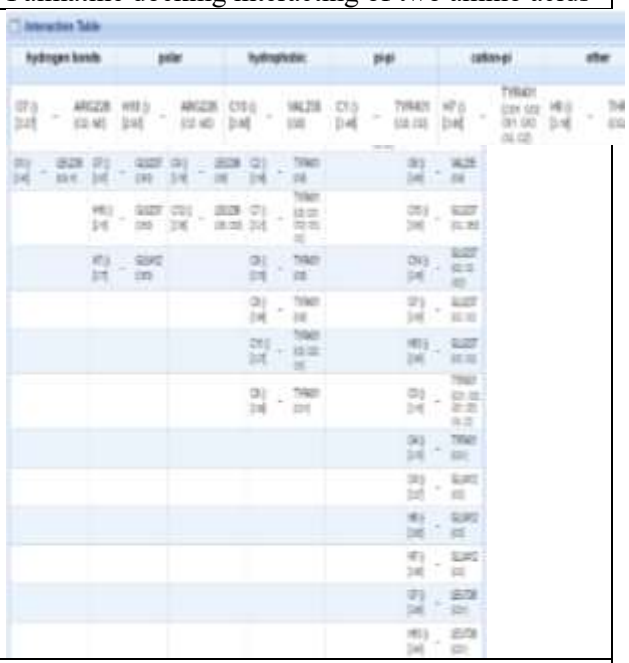
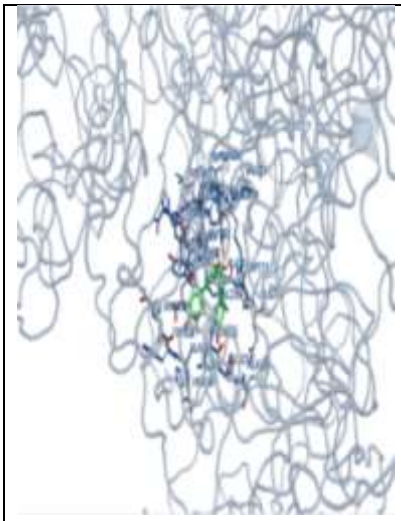
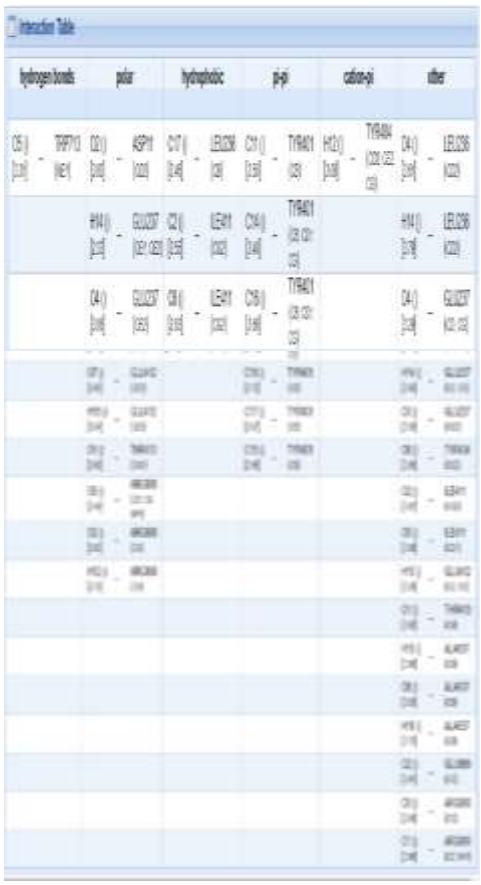
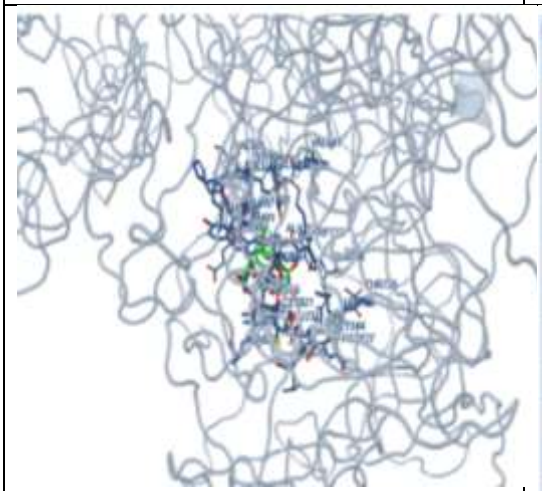
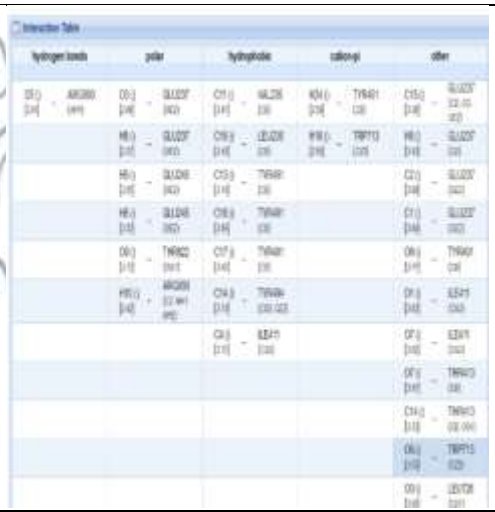
	
Quercetin docking	Quercetin docking interacting of two amino acids

	
Rosmarinic docking	Rosmarinic docking interacting of two amino acids
	
Syringin docking	Syringin docking interacting of two amino acids

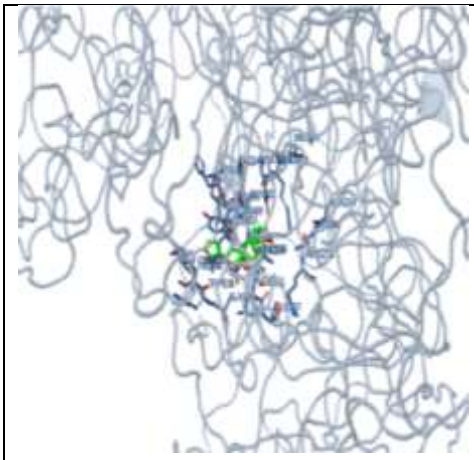
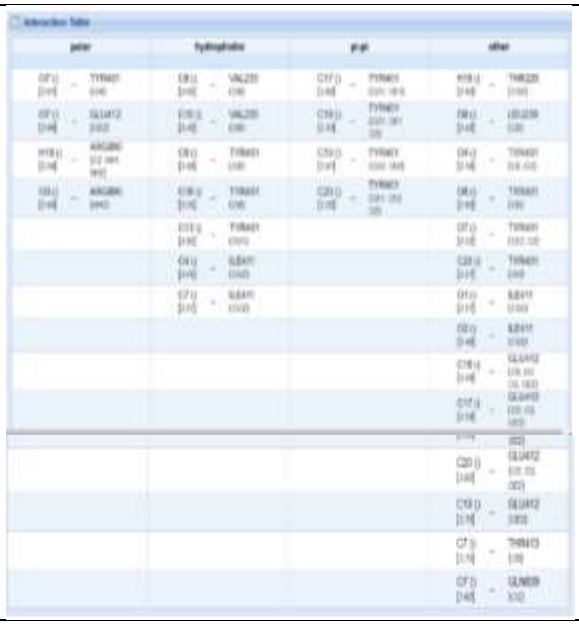
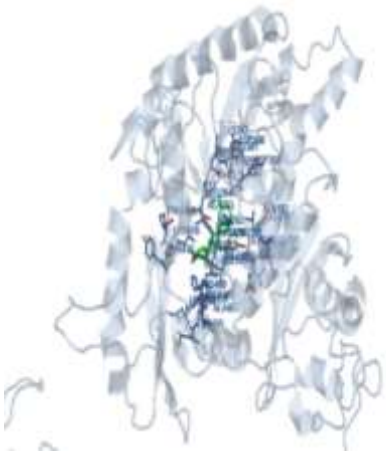
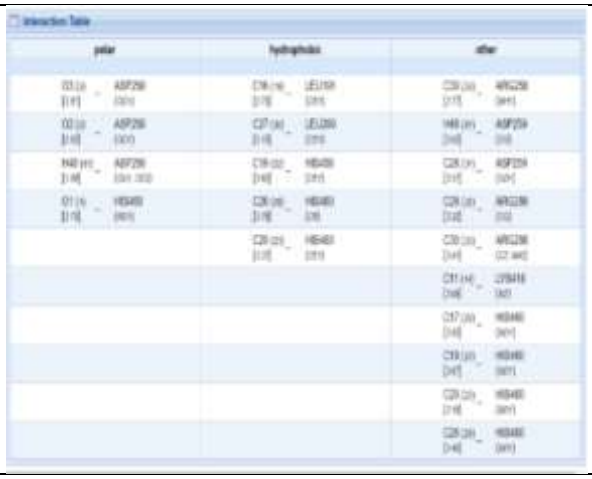
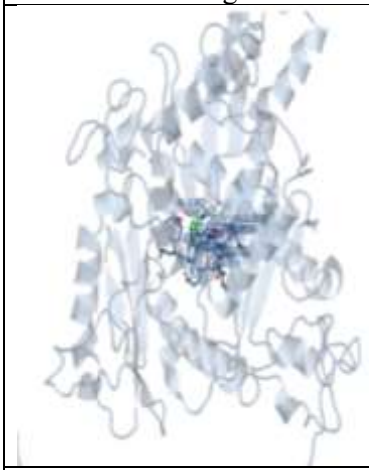
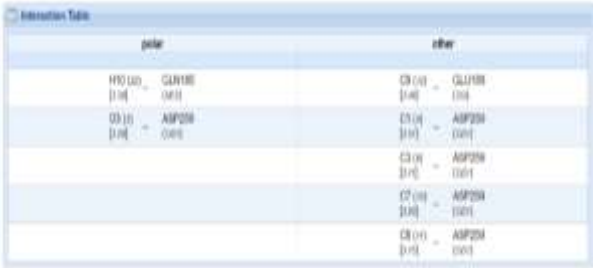
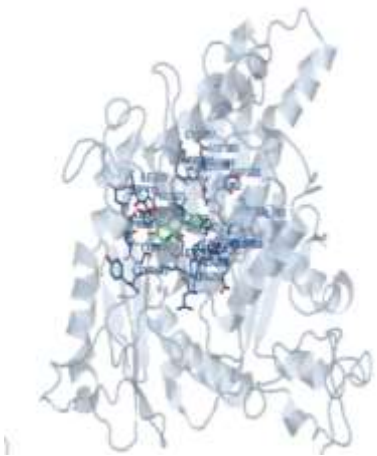
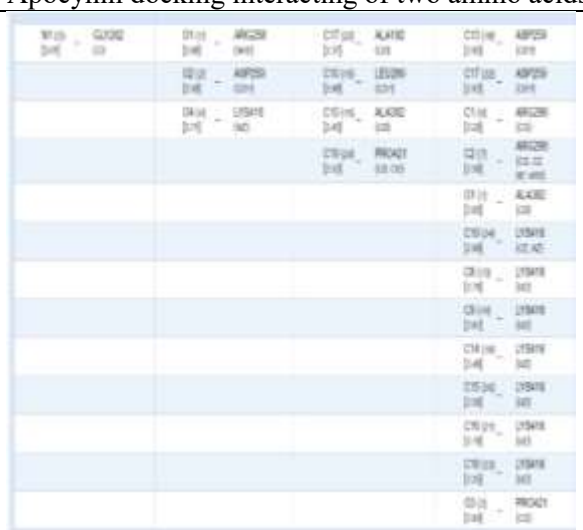
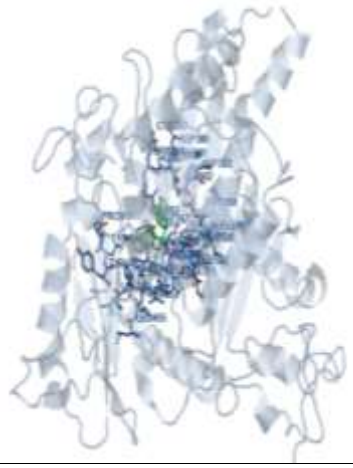
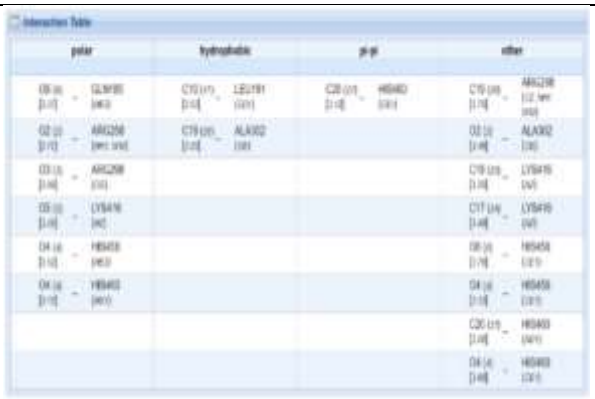
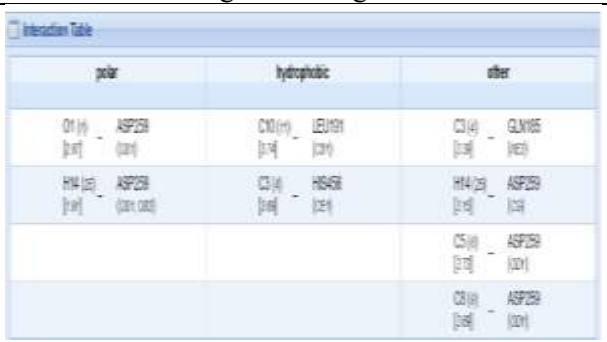
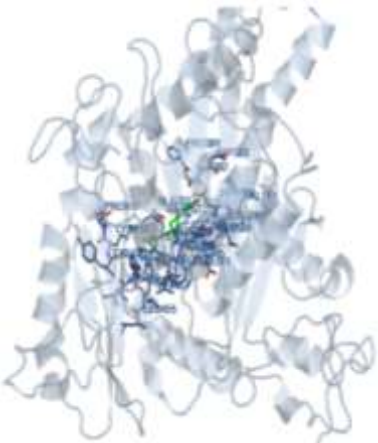
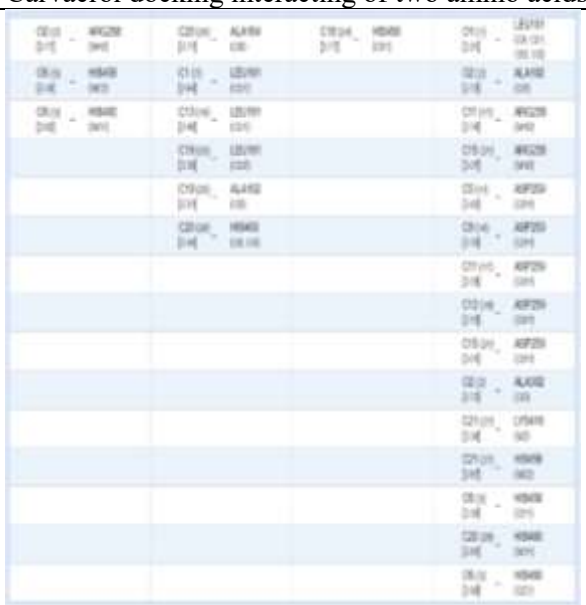
	
Tinosporide	Tinosporide docking interacting of two amino acids

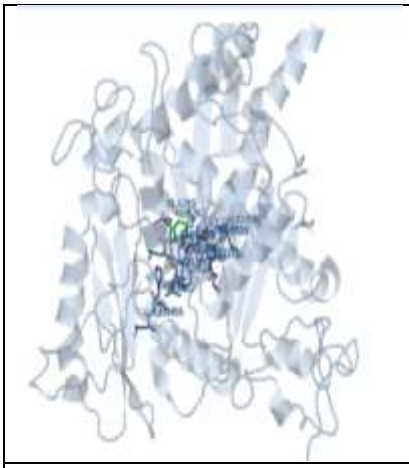
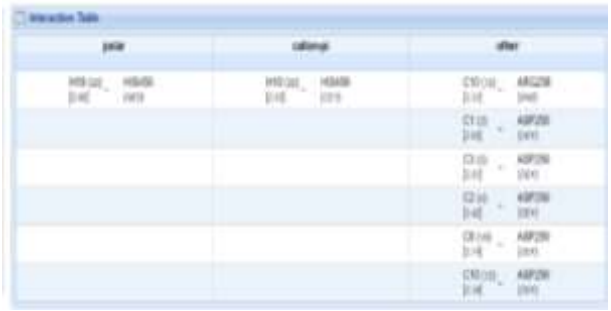
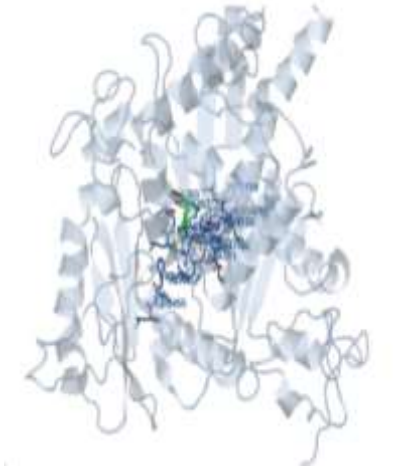
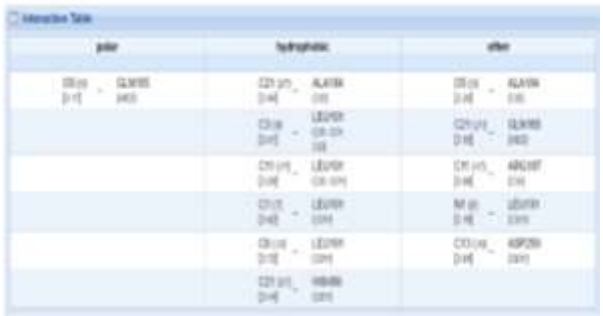
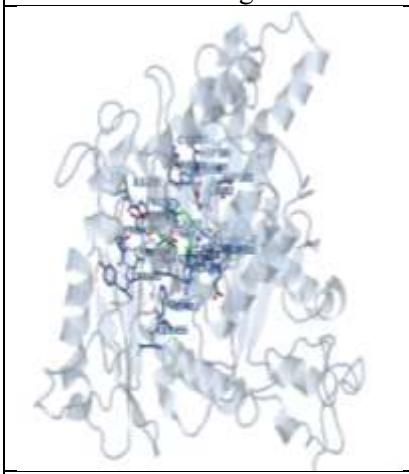
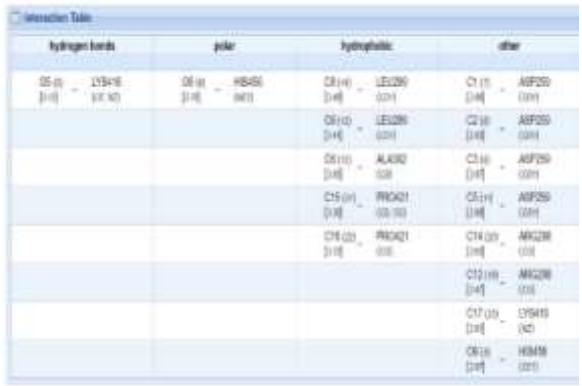
Table 6(a): Docking studies of MON1

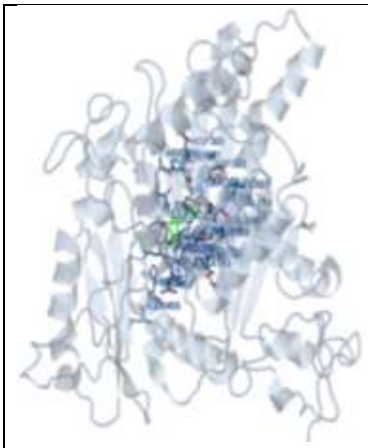
Phytocompound	Docking score	No.of interactions	Docking yes/no
Adlumine	-5.84	19	yes
Apocynin	-3.57	7	yes
Berberin	-5.03	21	yes
Bicuculine	-4.16	17	yes
Carvacrol	-4.01	8	Yes
Cryptopine	-4.33	25	yes
Eugenol	-3.92	8	yes
Fumaricine	-4.20	12	yes
Glycerides	-4.23	15	Yes
Isocolumbin	-5.28	23	Yes
Palmatine	-5.43	30	Yes
Quercetin	-4.63	11	yes
Rosmarinic	-3.73	13	yes
Syringin	-3.67	25	yes
Tinosporide	-5.48	15	yes

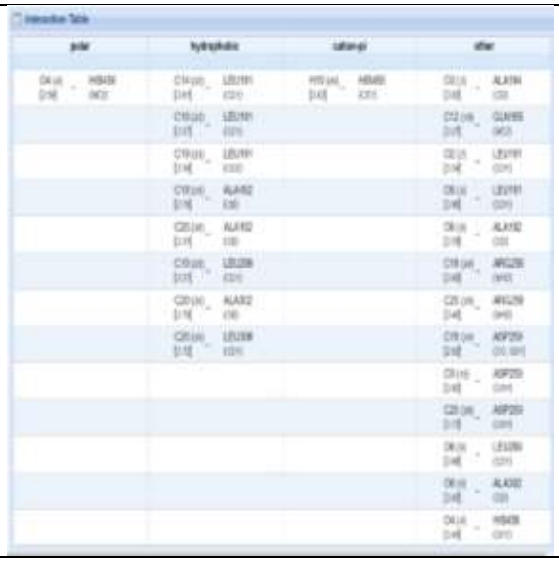
Table 6(b): Docking images and their interacted amino acid residues.

	
Adlumine docking	Adlumine docking interacting of two amino acids
	
Apocynin docking	Apocynin docking interacting of two amino acids
	
Berberin docking	Berberin docking interacting of two amino acids

	
Bicuculine docking	Bicuculine docking interacting of two amino acids
	
Carvacrol docking	Carvacrol docking interacting of two amino acids
	
Cryptopine docking	Cryptopine docking interacting of two amino acids

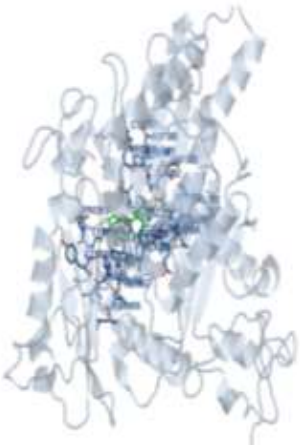
	
Eugenol docking	Eugenol docking interacting of two amino acids
	
Fumaricine docking	Fumaricine docking interacting of two amino acids
	
Glycerides docking	Glycerides docking interacting of two amino acids

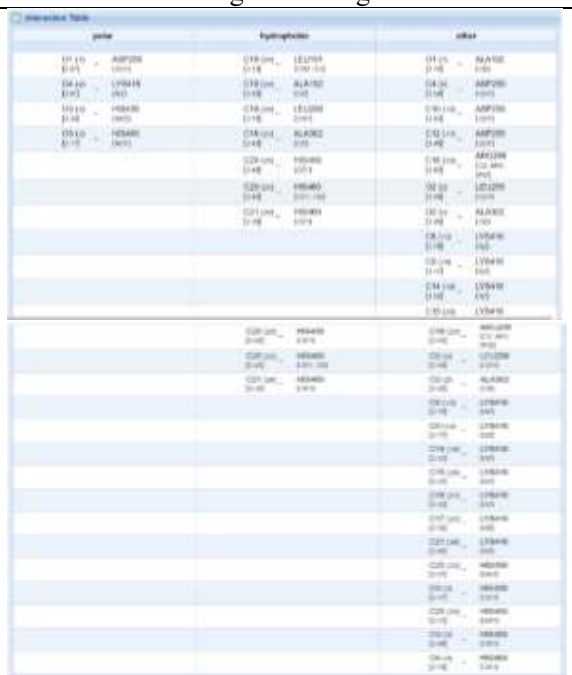




Isocolumbin docking

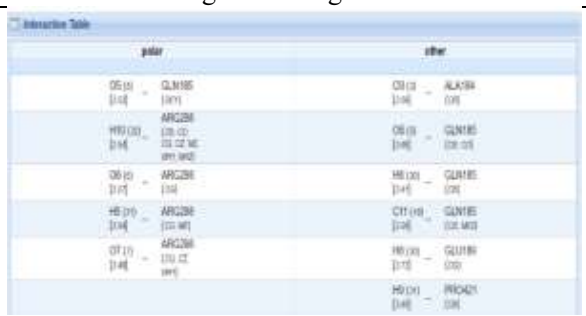
Isocolumbin docking interacting of two amino acids

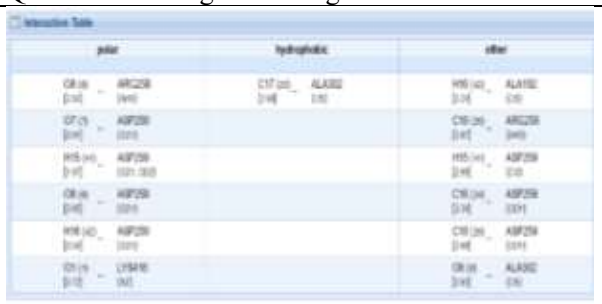
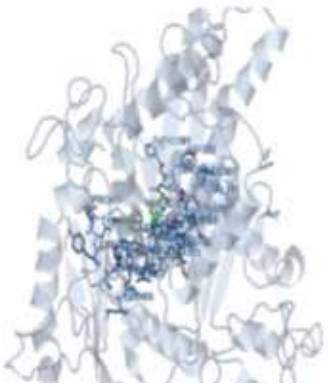
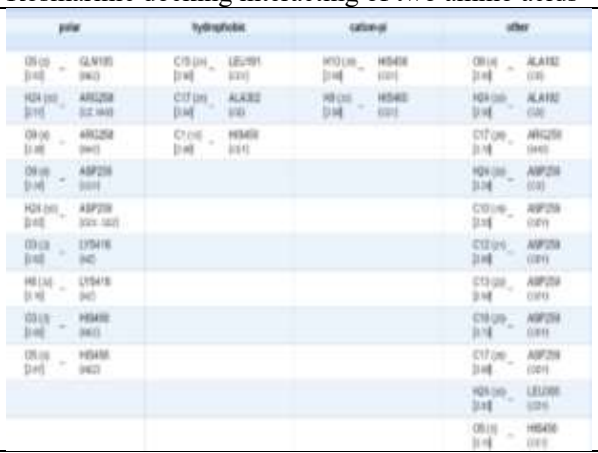




Palmatine docking

Palmatine docking interacting of two amino acids



Quercetin docking	Quercetin docking interacting of two amino acids
	
Rosmarinic docking	Rosmarinic docking interacting of two amino acids
	
Syringin docking	Syringin docking interacting of two amino acids
	
Tinosporide docking	Tinosporide docking interacting of two amino acids

4. Discussion

As per the results it is seen that MON1B docks with palmatine with a docking score of -5.43 kcal/mol with 30 interactions and CDK docks with palmatine with a docking score of -8.43 kcal/mol with 21 interactions. MON1B docks with syringin with docking score of -3.67 kcal/mol with 25 interactions and CDK docks with syringin with docking score of -4.54kcal/mol with 27 interactions. MON1b docks with cryptopine with docking score of -4.33 kcal/mol with 25 interactions. CDK docks with cryptopine with docking score

of 6.08 kcal/mol with 29 interactions. MON1b docks with berberine with docking score of 5.03 kcal/mol with 21 interactions. CDK docks with bernerin with docking score of -9.1kcal/mol with 33 interactions.

5. Conclusion

As per the results it is seen that phytocompounds palmatine, syringin, cryptopine with docking score of -4.33 kcal/mol with 25 interactions. Cdk8 docks with cryptopine with docking score of 6.08 kcal/mol with 29 interactions.

Mon1b docks with berberine with docking score of 5.03 kcal/mol with 21 interactions. Cdk8 docks with bernerin with docking score of -9.1kcal/mol with 33 interactions.

Hence the above compounds can be used as ligands for treating GERMAN MEASLES.

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