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In silico approach to combat HIV using phytoconstituents of *Moringa oleifera* Lam.

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ABSTRACT

HIV/AIDS remains a persistent problem around the world. There were approximately 35 million people worldwide living with HIV/AIDS in 2013. In Sub-Saharian Africa countries use of Moringa oleifera(MO)Lam. along with Antiretroviral (ART) regimen among HIV positive people is high. However, there is scarcity of scientific evidences to support M.oleifera as anti-HIV therapy. Recent research pointed out that the G protein-coupled chemokine receptor CXCR4 is an important target, as they are specifically implicated in cancer metastasis and HIV-1 infection. In present study, attempt has been made to answer the role of M.oleifera in HIV treatment using CXCR4 as a target receptor. Major phytoconstituents of MO incorporated in virtual screening against CXCR4. Drug molecule optimization, addition of charges and hydrogen bonds was carried out using Autodock tools. Receptor optimization was carried out using Accelrys Discovery studio visualizer 4. Molecular docking study was performed on Autodock 4.The results has shown that docking energy of 2-Pyrrolidinone (-3.35kcal/mol), Linalool oxide (-4.12kcal/mol), Upiol (-4.15kcal/mol), Beta Sitosterol (-6.12kcal/mol),1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester(-5.56 kcal/mol), Ellagic acid(-6.10 kcal/mol), Gallic acid (-4.38 kcal/mol), Ferulic acid (-4.81kcal/mol), Vanillin (-4.2 kcal/mol), 1,2,3-Cyclopentanetriol (-4.09 kcal/mol), Astragalin (-5.69kcal/mol), Aurantiamideacetate (-6.02kcal/mol), Chlorogenic acid (-5.89 kcal/mol), Isoquercetin (-5.52kcal/mol), Crypto-chlorogenic acid (-4.66 kcal/mol), Kaempferol (-5.90kcal/mol), Niaziminin (-3.96kcal/mol).6,6-dimethyl-5,6-dihydroimidazo[2,1-b][1,3]thiazol-3-yl)methyl-N,N'-dicyclohexylimidothiocarbamate and selected phytoconstituents of Moringa oleifera. Docking energies for (6,6-dimethyl-5,6-dihydroimidazo[2,1-b][1,3]thiazol-3-yl)methylN,N' dicyclohexyl imidothiocarbamate was taken as a standard ligand of CXCR4 for comparative study. Beta sitosterol, Ellagic acid and Aurantiamide acetate are shown as promising anti-HIV candidate. However, further in vitro and in vivo studies needed to validate their biological potential.

Keywords: HIV/AIDS, Moringa oleifera, CXCR4, virtual screening.

INTRODUCTION

Human immunodeficiency virus (HIV) is a retrovirus, belongs to the family of lentiviruses. HIV types 1 and 2 (HIV-1 and HIV-2) causes Acquired immunodeficiency syndrome (AIDS). During the course of AIDS in humans, immune system begins to fail which leads to life- threatening opportunistic infections or malignancies associated with the progressive failure of the immune system [1,2]. HIV/AIDS remains a persistent problem around the world. Till 2013, 35 million people were detected worldwide living with HIV/AIDS. Sub-Saharan Africa remains most severely affected due to HIV. In Sub-Saharan Africa, 1 in every 20 adults living with HIV. his accounts for nearly

71% of the people living with HIV worldwide [3].India is the third highest number of estimated people living with HIV in the world. According to the National AIDS Control Organisation (NACO) report 2014, the estimated number of people living with HIV/AIDS in India during 2012 were 20.89 lakh [4]. At present, there are no defined vaccines or drugs available to cure HIV infected patients. Currently, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) are anti-HIV class of drugs are exercised around the world [5].

Most HIV-infected patients in resource limited settings receive a first-line triple combination of lamivudine, nevirapine, stavudine or zidovudine. These combination antiretroviral therapy (ART) provides many benefits but it also creates more adverse events like peripheral neuropathy, hypersensitivity and life-threatening hepatotoxicity in HIV patients which hamper treatment adherence[6].

Chemokine receptors are critical regulators of cell migration in the context of immune surveillance, inflammation and development. In 2013, it is reported that G protein-coupled chemokine receptor CXCR4 isan important targets for HIV infection [7]. CXCR4 is a major co-receptor for T-cell-tropic HIV-1 [8]. Due to this, till now numerous efforts have been made to develop a new class of anti-HIV agents that target CXCR4 as an additional or alternative therapy to standard HAART. The first FDA approved CXCR4 antagonist, plerixafor/AMD3100 is used to mobilize hematopoietic stem cells, which are collected for use in stem cell graft in patients with hematological cancers. Plerixaforwas initially developed to interfere with SDF-1/CXCR4 interaction and shows promise for HIV infection, cancers and autoimmune diseases such as rheumatoid arthritis. However, this drug is expensive because of the difficulty in its total synthesis. Therefore, there is an urgent need for the discovery of new CXCR4 antagonists that are cost-effective, potent and safe[9]. Phytochemicals have been an important and safe source of lead compounds in drug discovery and development.

Moringa oleifera, Lam (*M. oleifera*) is a member of the Moringaceae family. This edible plant is also known as drumstick tree, horseradish tree and malunggay. *Moringa oleifera*, Lam is native to the sub-Himalayan tracts of India, Pakistan, Bangladesh and Afghanistan and it is consumed as food [10,11]. Phytochemical analyses have shown that *M. oleifera* leaves are particularly rich in potassium, calcium, phosphorous, iron, vitamins A and D, essential amino acids, as well as such known antioxidants such as β-carotene, vitamin C and flavonoids [12,13,14,15]. In many regions of Africa, from traditional days *M. oleifera* is widely consumed for self-medication by patients affected HIV/AIDS [16]. However, the benefit for the treatment or prevention of HIV disease or infection by using either dietary or topical administration of *M. oleifera* preparations are not quite well-known. There is room to exploit the potential *M. oleifera* in the battle against HIV. In the present study, attempt has been made to answer the role of *M.oleifera* in HIV treatment using CXCR4 as a target receptor.

EXPERIMENTAL SECTION

2.1. Data Set:
Phytoconstituents and standard drug compounds could be downloaded from the database (https://pubchem.ncbi.nlm.nih.gov/search/search.cgi) and generate the small molecule compounds to identify potential CXCR4 antagonist screening. A three-dimensional structure of CXCR4 chemokine GPCR protein could be offered from the Protein Data Bank (PDB ID: 3ODU)

2.2. Receptor Optimization:
Receptor was optimized using Discovery Studio version-4 Accelrys Software. The energy minimization of modeled protein was performed by SPDV and its score was obtained. Then the active sites of these proteins were obtained from online active site prediction tool. The Ramachandran plot was obtained to study the favorable regions with residues present.

2.3 Ligands Optimization:
Drug molecule and phytoconstituents optimization, addition of charges and hydrogen bonds was carried out using Autodock tools.

2.4 Computational Docking Studies:
The docking of selected protein with three drug molecules were performed by using Autodock 4. The docking calculations were verified using docking server [17]. Gasitier partial charges were added to ligand. Nonpolar hydrogen atoms were merged and rotatable hydrogen bonds were defined. Docking calculations were carried out on receptor. Essential hydrogen atoms, kollaman charges and savlavation parameters were added affinity (grid) maps 25 Å grid points and 0.500Å were generated using the autogrid program. Autodock parameters 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 Lamarckian algorithm (LGA) and Solis and Wet local search methods [18]. Initial position torsion and orientation of the drug molecules were set randomly. All rotatable torsions were released during docking. Each docking experiment was derived from 10 different runs that were set to terminate after 250000 energy calculations. The population size was set to 150. During search the translational step 0.2 Å and quaternion and torsion step 5 were applied [19].

RESULTS AND DISCUSSION

Docking is done by Autodock 4 for CXC4 structure with control drug(6,6-dimethyl-5,6-dihydroimidazo[2,1-b][1,3]thiazol-3-yl)methylN,N' dicyclohexylimidothiocarbamate and selected phytoconstituents of *Moringa oleifera.* Docking energies for (6,6-dimethyl-5,6-dihydroimidazo[2,1-b][1,3]thiazol-3-yl)methylN,N' dicyclohexylimidothiocarbamate (-9.17 Kcal/mol), 2-Pyrrolidinone (-3.35 kcal/mol), Linalool oxide (-4.12 kcal/mol), Upiol (-4.15 kcal/mol), 1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester (-5.56 kcal/mol), Ellagic acid (-6.10 kcal/mol), Gallic acid (-4.38 kcal/mol), Ferulic acid (-4.81 kcal/mol), Vanillin (-4.23 kcal/mol), 1,2,3-Cyclopentanetriol (-4.09 kcal/mol), Astragalin (-5.69 kcal/mol), Aurantiamideacetate (-6.02 kcal/mol), Chlorogenic acid (-5.89 kcal/mol), Isoquercetin (-5.52 kcal/mol), Crypto-chlorogenic acid (-4.66 kcal/mol), Kaempferol (-5.90 kcal/mol), Niaziminin (-3.96 kcal/mol), Beta Sitosterol(-6.12 kcal/mol) (Table **1**). Interaction tables of drug and all phytoconstituents has shown the non-covalent interactions occurring between active site residues and respective drug and phytoconstituents (Table **2-19**). The docking study showed that Beta sitosterol, Ellagic acid and Aurantiamide acetate as a promising anti-HIV candidate when they are compared with 6,6-dimethyl-5,6-dihydroimidazo[2,1-b][1,3]thiazol-3-yl)methylN,N' dicyclohexylimidothiocarbamate. However, further *in vitro* and *in vivo* studies of individual phytoconstituents is needed to validate their biological potential. Ball and socket model of respective drug molecule and phytoconstituents interacting with active site are shown in Fig. (**1-16**).

Table 1. CXCR4 chemokine GPCR inhibitors docked against 3ODU

Sr. No	**Drug molecule**	**Est. Free Energy of Binding** (kcal/mol)	**Estimated Inhibition Constant, Ki** (mM)	**vdW + Hbond + desolve Energy** (kcal/mol)	**Electrostatic Energy** (kcal/mol)	**Total Inter-molecular Energy** (kcal/mol)
1	6,6-dimethyl-5,6-dihydroimidazo[2,1-b][1,3]thiazol-3-yl)methyl-N,N'-dicyclohexyl imido thiocarbamate	-9.17	190.68	-8.42	-2.32	-10.74
2	2-Pyrrolidinone	-3.35	3.51	-3.33	-0.002	-3.35
3	Linalool oxide	-4.12	958.57	-5.62	-0.08	-5.69
4	Upiol	-4.15	905.78	-4.72	-0.08	-4.80
5	1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester	-5.56	84.15	-8.62	0	-8.62
6	Ellagic acid	-6.10	33.63	-5.63	-0.54	-6.17
7	Gallic acid	-4.38	616.49	-4.18	-0.43	-4.61
8	Ferulic acid	-4.81	299	-5.42	-0.01	-5.43
9	Vanillin	-4.23	793.80	-4.44	-0.06	-4.51
10	1,2,3-Cyclopentanetriol	-4.09	997.44	-4.14	-0.31	-4.45
11	Astragalin	-5.69	67.14	-5.59	-0.54	-6.63
12	Aurantiamideacetate	-6.02	38.98	-8.39	-0.26	-8.64
13	Chlorogenic acid	-5.89	47.86	-6.82	-0.64	-7.46
14	Isoquercetin	-5.52	63.07	-6.43	-0.50	-6.93
15	Crypto-chlorogenic acid	-4.66	384.07	-6.30	-0.27	-6.57
16	Kaempferol	-5.90	47.40	-6.16	-0.38	-6.53
17	Niaziminin	-3.96	1.25	-6.64	-0.05	-6.70
18.	Beta Sitosterol	-6.12	32.90	-7.70	-0.01	-7.71

Table 2. (6,6-dimethyl-5,6-dihydroimidazo[2,1-b][1,3]thiazol- 3-yl)methyl N,N'-dicyclohexylimidothiocarbamate interaction

Hydrogen bonds	Polar	Hydrophobic	Other
N2 () [*2.95*] – GLU32 (*CD, OE1, OE2*)	H1 () [*1.95*] – GLU32 (*OE1, OE2*)	C6 () [*3.42*] – LEU41 (*CD1*)	C17 () [*3.88*] – ARG30 (*CG*)
N4 () [2.58] – ASP97 (CG, OD1)	H3 () [2.01] – ASP97 (OD1)	C4 () [3.81] – LEU41 (CD1)	H1 () [2.58] – GLU32 (CD, CG)
N3 () [3.03] – ASP97 (OD1)	H2 () [3.57] – ASP97 (OD1)	C14 () [3.71] – TRP94 (CD1, CG)	C15 () [3.69] – GLU32 (OE1, OE2)
		C13 () [3.43] – TRP94 (CD2, CE2, CZ2)	S1 () [3.74] – GLU32 (OE2)
		C3 () [*3.31*] – TRP94 (*CE3, CZ3*)	C1 () [*3.84*] – TYR45 (*OH*)
		C4 () [*3.84*] – ALA98 (*CB*)	C3 () [*3.23*] – TYR45 (*OH*)
		C12 () [*3.02*] – TRP102 (*CE3, CH2, CZ3*)	C7 () [*3.41*] – TYR45 (*OH*)
		C14 () [*3.89*] – TRP102 (*CZ3*)	C4 () [*3.69*] – TYR45 (*OH*)
		C18 () [*3.79*] – ILE185 (*CG2*)	C13 () [*3.60*] – TRP94 (*NE1*)
		C15 () [*3.54*] – ILE185 (*CD1*)	H3 () [*3.01*] – ASP97 (*CB,CG*)
		C11 () [*3.51*] – CYS186 (*CB, SG*)	C12 () [*3.40*] – ASP97 (*CB, CG, OD1*)
			C19 () [*2.96*] – ASP97 (*OD1*)
			C21 () [*3.72*] – ASP97 (*OD1*)
			C1 () [*3.59*] – ASP97 (*OD1*)
			C5 () [*3.63*] – ASP97 (*OD1*)
			C11 () [*3.59*] – ASP97 (*OD1*)
			N2 () [*3.75*] – ILE185 (*CD1*)
			H1 () [*3.73*] – ILE185 (*CD1*)
			S1 () [*3.53*] – ILE185 (*CD1*)
			C8 () [*3.14*] – ASP187 (*OD2*)
			C9 () [*3.14*] – SER285 (*OG*)
			C6 () [*3.60*] – SER285 (*OG*)

Hydrogen bonds	Polar	Hydrophobic	Other
			C7 () [*3.47*] – GLU288 (*OE2*)

Table 3. 2-Pyrrolidinone interaction

Hydrogen bonds	Polar	Hydrophobic	Other
N () [*2.96*] – ASP97 (*CB, CG, OD1*)	H () [*2.19*] – ASP97 (*OD1*)	C () [*3.36*] – TRP94 (*CD1, CD2, CE2, CE3, CG*)	N () [*3.78*] – TRP94 (*CD2, CG*)
		C () [*3.28*] – TRP102 (*CZ3*)	O () [*3.73*] – TRP94 (*CD2, CE3, CZ3*)
		C () [*3.55*] – VAL112 (*CG2*)	C () [*3.65*] – TRP94 (*NE1*)
			C () [*3.28*] – ASP97 (*CB, CG, OD1*)
			H () [*2.91*] – ASP97 (*CB, CG*)

Table 4. Linalool oxide interaction

Polar	Hydrophobic	pi-pi	Other
O2 () [*3.13*] – ASP97 (*OD1*)	C8 () [*3.51*] – TRP94 (*CD1, CG*)	C2 () [*3.75*] – HIS113 (*CD2, CE1*)	O2 () [*3.78*] – TRP94 (*CD2, CE3*)
H1 () [*2.44*] – ASP97 (*OD1*)	C4 () [*3.42*] – TRP94 (*CD2, CE2, CZ2*)		C4 () [*3.73*] – TRP94 (*NE1*)
O1 () [*3.16*] – HIS113 (*NE2*)	C3 () [*3.55*] – TRP94 (*CH2, CZ2, CZ3*)		C8 () [*3.80*] – TRP94 (*NE1*)
	C5 () [*3.21*] – TRP94 (*CH2, CZ3*)		H1 () [*3.27*] – ASP97 (*CB, CG*)
	C10 () [*3.52*] – TRP102 (*CE3, CZ3*)		O2 () [*3.84*] – ASP97 (*CG*)
	C8 () [*3.52*] – TRP102 (*CZ3*)		C10 () [*3.18*] – ASP97 (*CG, OD1, OD2*)
	C9 () [*3.75*] – TRP102 (*CZ3*)		O1 () [*3.74*] – HIS113 (*CD2, CE1*)
	C8 () [*3.75*] – VAL112 (*CG2*)		C2 () [*3.41*] – HIS113 (*NE2*)
	C6 () [*3.39*] – HIS113 (*CD2*)		C6 () [*3.76*] – HIS113 (*NE2*)
	C6 () [*3.31*] – TYR116 (*CD2, CE2, CG*)		C5 () [*3.68*] – GLU288 (*OE1*)
	C10 () [*3.34*] – CYS186 (*CB, SG*)		
	C9 () [*3.56*] – CYS186 (*SG*)		

Table 5. Upiol interaction

Hydrogen bonds	Polar	Hydrophobic	cation-pi	Other
N2 () [*3.00*] – ASP97 (*CG, OD1*)	N1 () [*3.25*] – TRP94 (*NE1*)	C6 () [*3.58*] – TRP94 (*CD2, CG*)	H3 () [*2.65*] – TRP94 (*CB, CD2, CE2, CE3, CG, CZ3*)	N1 () [*3.08*] – TRP94 (*CD1, CD2, CE2, CE3, CG, CZ2*)
	H1 () [*2.94*] – TRP94 (*NE1*)	C5 () [*3.68*] – TRP94 (*CE2, CZ2*)	H1 () [*3.16*] – TRP94 (*CD1, CD2, CE2, CG, CZ2*)	N2 () [*3.57*] – TRP94 (*CD2, CE3, CG*)
	O2 () [*3.61*] – ASP97 (*OD1*)	C1 () [*3.39*] – HIS113 (*CE1*)		Br1 () [*3.37*] – TRP94 (*CH2, CZ2*)
	H2 () [*2.19*] – ASP97 (*OD1*)	C3 () [*3.24*] – HIS113 (*CE1*)		O2 () [*3.50*] – ASP97 (*CB, CG*)
	H3 () [*3.74*] – ASP97 (*OD1*)	C3 () [*3.23*] – CYS186 (*CB, SG*)		H2 () [*2.97*] – ASP97 (*CB, CG*)
	O1 () [*3.78*] – HIS113 (*ND1*)			C6 () [*3.70*] – ASP97 (*OD1*)
				O2 () [*3.27*] – TRP102 (*CZ3*)
				H1 () [*3.40*] – VAL112 (*CB, CG2*)
				O1 () [*3.36*] – VAL112 (*CG2*)
				O1 () [*3.75*] – HIS113 (*CE1*)
				C1 () [*3.46*] – HIS113 (*NE2*)
				C3 () [*3.86*] – HIS113 (*NE2*)

Table 6. 1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester interaction

Hydrogen bonds	Polar	Hydrophobic	Other
O4 () [*3.33*] – HIS113 (*CE1, NE2*)	O3 () [*3.65*] – ASP97 (*OD1*)	C16 () [*3.60*] – LEU41 (*CD1*)	C11 () [*2.96*] – TYR45 (*OH*)
	O1 () [*3.60*] – ASP97 (*OD1*)	C13 () [*3.57*] – TRP94 (*CD1, CD2, CG*)	C16 () [*3.09*] – TYR45 (*OH*)
	O4 () [*3.06*] – ASP187 (*OD1*)	C4 () [*3.59*] – TRP94 (*CE2, CZ2*)	C20 () [*3.86*] – ASP97 (*OD1*)
		C8 () [*3.53*] – TRP94 (*CZ2*)	C21 () [*3.27*] – ASP97 (*OD1*)
		C12 () [*3.46*] – TRP94 (*CH2, CZ2*)	C18 () [*3.48*] – ASP97 (*OD1*)
		C11 () [*3.68*] – TRP94 (*CZ3*)	C9 () [*3.61*] – HIS113 (*NE2*)
		C6 () [*3.36*] – TRP102 (*CZ3*)	C8 () [*3.84*] – HIS113 (*NE2*)
		C13 () [*3.85*] – TRP102 (*CZ3*)	C15 () [*3.53*] – HIS113 (*NE2*)
		C1 () [*3.64*] – VAL112 (*CG2*)	C22 () [*3.31*] – ASP187 (*CG, OD2*)
		C6 () [*3.88*] – VAL112 (*CG2*)	C17 () [*3.47*] – ASP187 (*CG, OD1*)
		C15 () [*3.45*] – HIS113 (*CD2*)	O4 () [*3.61*] – ASP187 (*CG*)
		C9 () [*3.12*] – HIS113 (*CE1*)	C24 () [*3.88*] – ASP187 (*OD2*)
		C1 () [*3.69*] – HIS113 (*CE1*)	C16 () [*3.28*] – SER285 (*CB, OG*)
		C8 () [*3.89*] – HIS113 (*CE1*)	C5 () [*3.85*] – GLU288 (*OE1, OE2*)
		C9 () [*3.63*] – CYS186 (*SG*)	C3 () [*3.31*] – GLU288 (*OE2*)
			C7 () [*3.64*] – GLU288 (*OE2*)
			C11 () [*3.20*] – GLU288 (*OE2*)

Table 7. Ellagic acid interaction

Hydrogen bonds	Polar	pi-pi	cation-pi	Other
O4 () [*2.87*] – SER285 (*CB, OG*)	O2 () [*3.47*] – TYR45 (*OH*)	C9 () [*3.55*] – TRP94 (*CB, CD2, CE3, CG*)	H1 () [*3.80*] – TRP94 (*CZ2*)	O2 () [*3.81*] – TRP94 (*CE3*)
	O7 () [*2.95*] – ASP97 (*OD1*)	C13 () [*3.74*] – TRP94 (*CD2, CG*)	H3 () [*3.49*] – TRP102 (*CH2, CZ3*)	O1 () [*3.59*] – TRP94 (*CH2, CZ2*)
	H1 () [*3.82*] – HIS113 (*ND1*)	C1 () [*3.19*] – TRP94 (*CD2, CE3, CH2, CZ3*)	H1 () [*3.72*] – HIS113 (*CE1*)	O7 () [*3.82*] – ASP97 (*CB, CG*)
	H2 () [*2.21*] – SER285 (*OG*)	C3 () [*3.18*] – TRP94 (*CD2, CE3, CZ3*)		C9 () [*3.05*] – ASP97 (*CB, CG, OD1*)
	O6 () [*3.81*] – SER285 (*OG*)	C8 () [*3.78*] – TRP94 (*CE2*)		C3 () [*3.27*] – ASP97 (*OD1*)
	H4 () [*2.15*] – GLU288 (*OE1, OE2*)	C2 () [*3.16*] – TRP94 (*CE3, CH2, CZ3*)		C12 () [*3.22*] – ASP97 (*OD1*)
	O4 () [*3.79*] – GLU288 (*OE2*)	C6 () [*3.59*] – TRP94 (*CE3, CH2, CZ2, CZ3*)		O7 () [*3.78*] – ALA98 (*CB*)
	H2 () [*3.63*] – GLU288 (*OE2*)	C12 () [*3.49*] – TRP94 (*CE3*)		O5 () [*3.29*] – TRP102 (*CH2, CZ3*)
	O6 () [*2.94*] – GLU288 (*OE2*)	C4 () [*3.59*] – TRP94 (*CH2, CZ3*)		H3 () [*2.79*] – VAL112 (*CB, CG2*)
		C5 () [*3.58*] – TRP94 (*CZ3*)		O3 () [*3.34*] – VAL112 (*CG2*)
		C11 () [*3.71*] – TRP94 (*CH2*)		H1 () [*3.78*] – VAL112 (*CG2*)
				O5 () [*3.73*] – VAL112 (*CG2*)
				O3 () [*3.77*] – HIS113 (*CE1*)
				H2 () [*3.14*] – SER285 (*CB*)
				C14 () [*2.92*] – GLU288 (*CD, OE2*)
				O6 () [*3.89*] – GLU288 (*CD*)
				H4 () [*3.05*] – GLU288 (*CD*)
				C10 () [*3.35*] – GLU288 (*OE1, OE2*)
				C7 () [*3.39*] – GLU288 (*OE2*)

Table 8. Gallic acid interaction

Polar			Hydrophobic			pi-pi			Other		
O2 () [*3.03*]	–	ASP97 (*OD1*)	C7 () [*3.44*]	–	TRP94 (*CH2, CZ2*)	C3 () [*3.62*]	–	TRP94 (*CD2, CE3*)	O2 () [*3.76*]	–	TRP94 (*CD2, CG*)
H2 () [*2.14*]	–	ASP97 (*OD1*)	C7 () [*3.89*]	–	HIS113 (*CD2*)	C5 () [*3.45*]	–	TRP94 (*CD2, CE2, CH2, CZ2*)	O4 () [*3.45*]	–	TRP94 (*CE2, CZ2*)
O1 () [*2.96*]	–	ASP97 (*OD1*)				C1 () [*3.38*]	–	TRP94 (*CE2, CH2, CZ2, CZ3*)	O2 () [*3.61*]	–	ASP97 (*CB, CG*)
H1 () [*2.01*]	–	ASP97 (*OD1*)				C2 () [*3.75*]	–	TRP94 (*CE3, CZ3*)	H2 () [*2.88*]	–	ASP97 (*CB, CG*)
O5 () [*3.53*]	–	HIS113 (*NE2*)				C4 () [*3.68*]	–	TRP94 (*CZ3*)	H1 () [*3.21*]	–	ASP97 (*CG*)
						C6 () [*3.51*]	–	TRP94 (*CH2, CZ3*)	C2 () [*3.72*]	–	ASP97 (*OD1*)
									C3 () [*3.75*]	–	ASP97 (*OD1*)
									O4 () [*3.87*]	–	VAL112 (*CG2*)
									O5 () [*3.33*]	–	HIS113 (*CD2, CG*)
									C7 () [*3.87*]	–	HIS113 (*NE2*)
									O4 () [*3.76*]	–	TYR116 (*CB*)
									O5 () [*3.78*]	–	TYR116 (*CD2, CG*)

Table 9. Aurantiamideacetate interaction

Polar	Hydrophobic	pi-pi	cation-pi	Other
O2 () [*3.17*] – HIS113 (*NE2*)	C25 () [*3.71*] – LEU41 (*CD1*)	C27 () [*3.67*] – TYR45 (*CE2*)	H2 () [*3.78*] – TRP94 (*CZ3*)	C27 () [*3.40*] – TYR45 (*OH*)
O2 () [*3.79*] – ARG188 (*NH1*)	C27 () [*3.76*] – LEU41 (*CD1*)	C26 () [*3.53*] – TYR45 (*CE2*)		C26 () [*3.44*] – TYR45 (*OH*)
O4 () [*3.41*] – ARG188 (*NH1, NH2*)	C27 () [*3.24*] – ALA98 (*CB*)	C17 () [*3.30*] – TRP94 (*CD1, CD2, CE2, CG, CZ2*)		C17 () [*3.25*] – TRP94 (*NE1*)
	C26 () [*3.74*] – ALA98 (*CB*)	C20 () [*3.58*] – TRP94 (*CD1, CG*)		C20 () [*3.76*] – TRP94 (*NE1*)
	C17 () [*3.52*] – VAL112 (*CG2*)	C23 () [*3.84*] – TRP94 (*CE3*)		C18 () [*3.51*] – ASP97 (*CB, CG, OD1*)
	C20 () [*3.74*] – VAL112 (*CG2*)	C18 () [*3.19*] – TRP102 (*CE3, CZ3*)		C13 () [*3.31*] – ASP97 (*CG, OD1*)
	C4 () [*3.35*] – HIS113 (*CE1*)	C20 () [*3.73*] – TRP102 (*CZ3*)		C11 () [*3.65*] – ASP97 (*OD1*)
	C9 () [*3.78*] – ILE284 (*CG2*)	C19 () [*3.75*] – HIS281 (*CE1*)		C16 () [*3.35*] – ASP97 (*OD1*)
	C14 () [*3.16*] – ILE284 (*CG2*)			C26 () [*3.65*] – ASP97 (*OD1*)
				C23 () [*3.02*] – ASP97 (*OD1*)
				O2 () [*3.81*] – HIS113 (*CD2*)
				C4 () [*3.52*] – HIS113 (*NE2*)
				C19 () [*3.04*] – SER285 (*OG*)
				C15 () [*2.82*] – SER285 (*OG*)
				C10 () [*3.86*] – SER285 (*OG*)
				C3 () [*2.90*] – GLU288 (*CD, OE1, OE2*)
				C7 () [*3.13*] – GLU288 (*CD, OE1, OE2*)
				C9 () [*3.81*] – GLU288 (*OE2*)
				C10 () [*3.50*] – GLU288 (*OE2*)

Table 10. Chlorogenic acid interaction

Polar	Hydrophobic	pi-pi	cation-pi	Other
O8 () [*2.95*] – ASP97 (*OD1*)	C9 () [*3.86*] – TRP94 (*CH2*)	C15 () [*3.50*] – TRP94 (*CD2, CE2, CZ2*)	H5 () [*3.83*] – TRP102 (*CZ3*)	C15 () [*3.57*] – TRP94 (*NE1*)
H4 () [*2.06*] – ASP97 (*OD1, OD2*)	C10 () [*3.89*] – TRP94 (*CH2*)	C13 () [*3.25*] – TRP94 (*CE2, CH2, CZ2*)		C13 () [*3.78*] – TRP94 (*NE1*)
O9 () [*3.37*] – ASP97 (*OD1*)	C15 () [*3.61*] – VAL112 (*CG2*)	C11 () [*3.84*] – TRP94 (*CH2, CZ2*)		H4 () [*2.89*] – ASP97 (*CB, CG*)
H5 () [*2.41*] – ASP97 (*OD1, OD2*)	C10 () [*3.79*] – HIS113 (*CD2*)	C11 () [*3.90*] – HIS113 (*CE1*)		O9 () [*3.58*] – ASP97 (*CB, CG*)
O1 () [*3.54*] – TYR116 (*OH*)	C8 () [*3.58*] – TYR116 (*CE2*)			H5 () [*2.74*] – ASP97 (*CB, CG*)
O7 () [*3.17*] – ARG188 (*CZ, NH1, NH2*)				O8 () [*3.77*] – ASP97 (*CG*)
O2 () [*2.98*] – GLN200 (*NE2, OE1*)				O9 () [*3.40*] – TRP102 (*CZ3*)
H1 () [*2.20*] – GLN200 (*NE2, OE1*)				C10 () [*3.63*] – HIS113 (*NE2*)
O5 () [*3.17*] – GLN200 (*OE1*)				C11 () [*3.78*] – HIS113 (*NE2*)
O2 () [*2.91*] – TYR255 (*OH*)				O7 () [*3.63*] – TYR116 (*CD2, CE2*)
H1 () [*3.71*] – TYR255 (*OH*)				O1 () [*3.51*] – TYR116 (*CE2, CZ*)
O1 () [*3.29*] – GLU288 (*OE1*)				O2 () [*3.75*] – GLN200 (*CD*)
O3 () [*2.92*] – GLU288 (*OE1, OE2*)				H1 () [*3.15*] – GLN200 (*CD*)
H2 () [*2.01*] – GLU288 (*OE1, OE2*)				C1 () [*3.48*] – TYR255 (*OH*)
H3 () [*2.60*] – GLU288 (*OE1, OE2*)				C3 () [*3.81*] – TYR255 (*OH*)
O4 () [*3.49*] – GLU288 (*OE2*)				C4 () [*3.19*] – TYR255 (*OH*)
				O4 () [*3.08*] – ILE284 (*CG2*)
				H3 () [*3.72*] – ILE284 (*CG2*)
				C5 () [*2.97*] – GLU288 (*CD, OE1, OE2*)
				O3 () [*3.41*] – GLU288 (*CD*)
				H2 () [*2.70*] – GLU288 (*CD*)
				H3 () [*3.21*] – GLU288 (*CD*)
				C2 () [*3.70*] – GLU288 (*OE1*)

Table 11. Isoquercetin interaction

Hydrogen bonds	Polar	Hydrophobic	pi-pi	cation-pi	Other
O10 () [*2.79*] – TYR255 (*CE1, CZ, OH*)	H3 () [*3.87*] – TYR45 (*OH*)	C13 () [*3.72*] – ILE284 (*CG2*)	C20 () [*3.66*] – TRP94 (*CH2, CZ2*)	H8 () [*3.08*] – HIS113 (*CB, CD2, CE1, CG*)	O5 () [*3.86*] – LEU41 (*CD1*)
O8 () [*3.07*] – SER285 (*OG*)	O1 () [*3.35*] – ASP97 (*OD1*)	C17 () [*3.05*] – ILE284 (*CG2*)	C16 () [*3.36*] – TRP94 (*CH2, CZ2*)	H6 () [*2.95*] – TYR255 (*CE1, CZ*)	O6 () [*3.48*] – ASP97 (*CG*)
O9 () [*2.96*] – SER285 (*CB, OG*)	O6 () [*3.06*] – ASP97 (*OD1, OD2*)		C8 () [*3.87*] – TRP94 (*CZ3*)		H4 () [*2.59*] – ASP97 (*CG*)
	H4 () [*2.24*] – ASP97 (*OD1, OD2*)		C12 () [*3.60*] – TRP94 (*CH2, CZ3*)		C4 () [*3.47*] – ASP97 (*OD1*)
	H2 () [*3.85*] – ASP97 (*OD1*)		C20 () [*3.85*] – HIS113 (*CD2*)		C2 () [*3.06*] – ASP97 (*OD1*)
	O12 () [*3.22*] – HIS113 (*ND1, NE2*)		C21 () [*3.57*] – HIS113 (*CE1*)		C1 () [*3.88*] – ASP97 (*OD1*)
	H8 () [*2.92*] – HIS113 (*ND1, NE2*)				C3 () [*3.84*] – ASP97 (*OD1*)
	H2 () [*3.38*] – ARG183 (*CZ, NH1, NH2*)				C6 () [*3.49*] – ASP97 (*OD1*)
	O6 () [*3.64*] – ARG183 (*NH1*)				O3 () [*3.85*] – ALA98 (*CB*)
	H4 () [*3.43*] – ARG183 (*NH1*)				H7 () [*3.63*] – VAL112 (*CG2*)
	H6 () [*2.20*] – TYR255 (*OH*)				O12 () [*3.15*] – VAL112 (*CG2*)
	H3 () [*3.57*] – SER285 (*OG*)				H8 () [*3.34*] – VAL112 (*CG2*)
	H5 () [*2.30*] – SER285 (*OG*)				O12 () [*3.22*] – HIS113 (*CE1, CG*)
	O7 () [*3.61*] – GLU288 (*OE1*)				C21 () [*3.67*] – HIS113 (*NE2*)
	O8 () [*3.74*] – GLU288 (*OE2*)				C20 () [*3.70*] – HIS113 (*NE2*)
	H5 () [*3.62*] – GLU288 (*OE2*)				H2 () [*3.70*] – ILE185 (*CD1*)
					C18 () [*3.69*] – TYR255 (*OH*)
					O10 () [*3.81*] – ILE259 (*CD1*)
					H6 () [*3.13*] – ILE259 (*CD1*)
					O9 () [*3.43*] – ILE284 (*CG2*)
					H6 () [*3.73*] – ILE284 (*CG2*)
					H5 () [*3.22*] – SER285 (*CB*)
					C10 () [*3.10*] – GLU288 (*CD, OE2*)
					C11 () [*3.43*] – GLU288 (*CD, OE1, OE2*)
					C14 () – GLU288

Hydrogen bonds	Polar	Hydrophobic	pi-pi	cation-pi	Other
					[*3.52*] (*OE1*)
					C7 () [*3.86*] – GLU288 (*OE2*)
					C9 () [*3.32*] – GLU288 (*OE2*)
					C13 () [*3.47*] – GLU288 (*OE2*)

Table 12. Crypto-chlorogenic acid interaction

Polar	Hydrophobic	pi-pi	cation-pi	Other
O4 () [*3.71*] – GLU32 (*OE2*)	C3 () [*3.31*] – ALA98 (*CB*)	C16 () [*3.89*] – TRP94 (*CZ2*)	H4 () [*3.42*] – TRP94 (*CE2, CZ2*)	O5 () [*3.77*] – GLU32 (*CB*)
O8 () [*3.73*] – TRP94 (*NE1*)		C15 () [*3.78*] – HIS113 (*CD2, CE1*)	H5 () [*2.99*] – HIS113 (*CB, CD2, CE1, CG*)	O4 () [*3.90*] – GLU32 (*CD*)
H4 () [*3.40*] – TRP94 (*NE1*)		C16 () [*3.73*] – HIS113 (*CE1*)	H5 () [*3.75*] – TYR116 (*CB, CG*)	C4 () [*3.66*] – GLU32 (*OE2*)
O1 () [*3.69*] – ASP97 (*OD1*)				C6 () [*3.64*] – GLU32 (*OE2*)
O7 () [*3.57*] – ASP97 (*OD1*)				O2 () [*3.42*] – LYS38 (*CE*)
O3 () [*3.28*] – ASP97 (*OD1*)				H1 () [*3.43*] – LYS38 (*CE*)
H2 () [*2.48*] – ASP97 (*OD1*)				O8 () [*3.63*] – TRP94 (*CE2, CZ2*)
H5 () [*3.32*] – HIS113 (*ND1, NE2*)				O9 () [*3.49*] – TRP94 (*CZ2*)
O6 () [*3.82*] – SER285 (*OG*)				H2 () [*3.27*] – ASP97 (*CB, CG*)
				C2 () [*3.56*] – ASP97 (*OD1*)
				C8 () [*3.24*] – ASP97 (*OD1*)
				C9 () [*2.97*] – ASP97 (*OD1*)
				O3 () [*3.26*] – ALA98 (*CB*)
				H2 () [*3.26*] – ALA98 (*CB*)
				H4 () [*3.24*] – VAL112 (*CB, CG2*)
				O8 () [*3.54*] – VAL112 (*CG2*)
				O9 () [*3.81*] – HIS113 (*CD2*)
				C16 () [*3.56*] – HIS113 (*NE2*)
				C15 () [*3.28*] – HIS113 (*NE2*)
				C13 () [*3.75*] – HIS113 (*NE2*)
				O9 () [*3.86*] – TYR116 (*CB*)

Polar	Hydrophobic	pi-pi	cation-pi	Other
				O4 () [*3.76*] – ILE185 (*CD1*)
				H3 () [*3.63*] – ILE185 (*CD1*)

Table 13. Kaempferol interaction

Polar	pi-pi	cation-pi	Other
O3 () [*3.82*] – TRP94 (*NE1*)	C7 () [*3.60*] – TRP94 (*CD2, CE2, CE3*)	H1 () [*3.29*] – TRP94 (*CD1, CD2, CE2, CZ2*)	O3 () [*3.76*] – TRP94 (*CE2*)
H1 () [*3.28*] – TRP94 (*NE1*)	C10 () [*3.54*] – TRP94 (*CD2, CE3*)	H3 () [*3.44*] – TYR255 (*CZ*)	O4 () [*3.82*] – TRP94 (*CZ2*)
O5 () [*2.93*] – ASP97 (*OD1*)	C1 () [*3.42*] – TRP94 (*CE2, CE3, CH2, CZ2, CZ3*)		O1 () [*3.57*] – TRP94 (*CH2, CZ3*)
H2 () [*2.01*] – ASP97 (*OD1*)	C2 () [*3.25*] – TRP94 (*CE3, CH2, CZ3*)		H2 () [*3.19*] – ASP97 (*CB, CG*)
O4 () [*3.74*] – HIS113 (*ND1, NE2*)	C8 () [*3.34*] – TRP94 (*CE3, CZ3*)		C9 () [*3.32*] – ASP97 (*OD1*)
O2 () [*3.78*] – HIS113 (*NE2*)	C9 () [*3.46*] – TRP94 (*CE3, CZ3*)		C10 () [*3.20*] – ASP97 (*OD1*)
O6 () [*3.03*] – TYR255 (*OH*)	C4 () [*3.50*] – TRP94 (*CH2, CZ2*)		O3 () [*3.80*] – VAL112 (*CG2*)
H3 () [*2.10*] – TYR255 (*OH*)	C5 () [*3.70*] – TRP94 (*CH2, CZ2*)		H1 () [*3.42*] – VAL112 (*CG2*)
	C3 () [*3.64*] – TRP94 (*CH2*)		O2 () [*3.40*] – HIS113 (*CD2*)
	C14 () [*3.60*] – TYR116 (*CE2*)		O4 () [*3.63*] – HIS113 (*CE1*)
	C12 () [*3.38*] – TYR116 (*CE2*)		O2 () [*3.25*] – TYR116 (*CB, CD2, CE2, CG*)
			C12 () [*3.80*] – ARG188 (*NH1, NH2*)
			C14 () [*3.57*] – ARG188 (*NH2*)
			C13 () [*3.86*] – TYR255 (*OH*)
			C15 () [*3.77*] – TYR255 (*OH*)
			C11 () [*2.94*] – GLU288 (*CD, OE1, OE2*)
			C6 () [*3.74*] – GLU288 (*OE1*)
			C13 () [*3.23*] – GLU288 (*OE1*)

Table 14. Niaziminin interaction

Hydrogen bonds	Polar	Hydrophobic	Other
N1 () – GLN200 (*OE1*) [*3.44*]	O3 () – ASP97 (*OD1*) [*3.02*]	C11 () – TRP102 (*CZ3*) [*3.74*]	O6 () – TRP94 (*CD2, CE3, CG*) [*3.47*]
	H1 () – ASP97 (*OD1*) [*2.13*]	C11 () – CYS186 (*SG*) [*3.82*]	H1 () – ASP97 (*CB, CG*) [*3.29*]
	O2 () – ASP97 (*OD1*) [*3.40*]	C19 () – PHE199 (*CB*) [*3.50*]	C8 () – ASP97 (*CG, OD1*) [*3.13*]
	O6 () – ASP97 (*OD1*) [*3.50*]		C11 () – ASP97 (*CG, OD1*) [*3.32*]
	O4 () – SER285 (*OG*) [*3.89*]		C2 () – ASP97 (*OD1*) [*3.73*]
	O5 () – SER285 (*OG*) [*3.77*]		C18 () – ARG188 (*NH2*) [*3.55*]
	H2 () – SER285 (*OG*) [*2.95*]		S1 () – GLN200 (*CD, NE2, OE1*) [*3.34*]
	O4 () – GLU288 (*OE2*) [*3.02*]		C16 () – GLN200 (*OE1*) [*3.48*]
			C17 () – GLN200 (*OE1*) [*3.38*]
			C9 () – GLU288 (*CD, OE1, OE2*) [*2.90*]
			C7 () – GLU288 (*OE2*) [*3.35*]

Table 15. Ferulic acid interaction

Polar	Hydrophobic	pi-pi	cation-pi	Other
O4 (*4*) – TRP94 (*NE1*) [*3.75*]	C10 (*14*) – TRP94 (*CD1, CG*) [*3.58*]	C1 (*5*) – TRP94 (*CH2, CZ2*) [*3.68*]	H1 (*15*) – HIS113 (*CD2*) [*3.62*]	O4 (*4*) – PHE93 (*CB*) [*3.23*]
O3 (*3*) – ASP97 (*OD1*) [*3.37*]	C8 (*12*) – TRP94 (*CD1, CE2*) [*3.59*]	C4 (*8*) – TRP94 (*CZ2*) [*3.51*]	H1 (*15*) – TYR116 (*CD2, CE2*) [*3.72*]	O4 (*4*) – TRP94 (*CD1, CG*) [*3.29*]
O1 (*1*) – HIS113 (*NE2*) [*3.74*]	C7 (*11*) – TRP94 (*CE2, CZ2*) [*3.74*]	C5 (*9*) – HIS113 (*CD2, CG*) [*3.05*]		C8 (*12*) – TRP94 (*NE1*) [*3.50*]
O2 (*2*) – ARG188 (*CZ, NH1, NH2*) [*3.59*]	C10 (*14*) – TRP102 (*CZ3*) [*3.57*]	C6 (*10*) – HIS113 (*CD2, CG*) [*3.27*]		C10 (*14*) – TRP94 (*NE1*) [*3.83*]
H1 (*15*) – ARG188 (*CZ, NH1, NH2*) [*2.99*]	C8 (*12*) – VAL112 (*CG2*) [*3.31*]	C2 (*6*) – HIS113 (*CD2*) [*3.51*]		O3 (*3*) – ASP97 (*CB, CG*) [*3.53*]
O1 (*1*) – ARG188 (*NH1*) [*3.18*]	C10 (*14*) – VAL112 (*CG2*) [*3.77*]	C4 (*8*) – HIS113 (*CD2*) [*3.88*]		O3 (*3*) – TRP102 (*CZ3*) [*3.62*]
		C1 (*5*) – HIS113 (*CE1*) [*3.89*]		O4 (*4*) – TRP102 (*CH2, CZ3*) [*3.34*]
		C6 (*10*) – TYR116 (*CB, CD2, CG*) [*3.32*]		O4 (*4*) – VAL112 (*CB, CG2*) [*3.52*]
		C5 (*9*) – TYR116 (*CD2*) [*3.60*]		O2 (*2*) – HIS113 (*CD2*) [*3.26*]
				C1 (*5*) – HIS113 (*NE2*) [*3.86*]
				C2 (*6*) – HIS113 (*NE2*) [*3.27*]
				C3 (*7*) – HIS113

Polar	Hydrophobic	pi-pi	cation-pi	Other
				[*3.51*] (*NE2*)
				C5 (*9*) [*3.36*] – HIS113 (*NE2*)
				C6 (*10*) [*3.71*] – HIS113 (*NE2*)
				C9 (*13*) [*3.81*] – HIS113 (*NE2*)
				O2 (*2*) [*3.12*] – TYR116 (*CD2, CE2, CG*)
				C9 (*13*) [*3.79*] – ASP187 (*OD1*)
				C9 (*13*) [*3.23*] – ARG188 (*NH1*)

Table 16. Vanillin interaction

Polar	Hydrophobic	pi-pi	Other
O1 (*1*) [*3.43*] – ASP97 (*OD1*)	C8 (*11*) [*3.45*] – TRP94 (*CE3, CZ3*)	C4 (*7*) [*3.69*] – TRP94 (*CD2, CE2, CG*)	O2 (*2*) [*3.81*] – TRP94 (*CG*)
O2 (*2*) [*3.12*] – ASP97 (*OD1*)	C7 (*10*) [*3.83*] – TRP94 (*CZ2*)	C6 (*9*) [*3.46*] – TRP94 (*CD1, CD2, CE2, CG*)	C5 (*8*) [*3.32*] – TRP94 (*NE1*)
H1 (*12*) [*2.30*] – ASP97 (*OD1*)	C5 (*8*) [*3.06*] – VAL112 (*CB, CG2*)	C2 (*5*) [*3.47*] – TRP94 (*CE2, CZ2*)	C6 (*9*) [*3.27*] – TRP94 (*NE1*)
O3 (*3*) [*3.71*] – HIS113 (*NE2*)	C6 (*9*) [*3.37*] – VAL112 (*CG2*)	C5 (*8*) [*3.43*] – TRP94 (*CE2, CZ2*)	O2 (*2*) [*3.51*] – ASP97 (*CB, CG*)
	C7 (*10*) [*3.51*] – HIS113 (*CD2, CE1, CG*)	C3 (*6*) [*3.80*] – TRP94 (*CH2, CZ2*)	H1 (*12*) [*2.95*] – ASP97 (*CB, CG*)
	C7 (*10*) [*3.72*] – TYR116 (*CB*)		C8 (*11*) [*3.75*] – ASP97 (*OD1*)
			O3 (*3*) [*3.41*] – HIS113 (*CD2, CG*)
			C7 (*10*) [*3.72*] – HIS113 (*ND1, NE2*)
			O3 (*3*) [*3.50*] – TYR116 (*CB, CD2, CG*)

Table 17. 1,2,3-Cyclopentanetriol interaction

Polar	Hydrophobic	Other
O () [*3.00*] – ASP97 (*OD1*)	C () [*3.46*] – TRP94 (*CD1, CD2, CE2, CE3, CG*)	O () [*3.75*] – TRP94 (*CE3, CG*)
H () [*2.03*] – ASP97 (*OD1, OD2*)	C () [*3.39*] – VAL112 (*CG2*)	H () [*2.76*] – ASP97 (*CB, CG*)
	C () [*3.55*] – HIS113 (*CE1*)	O () [*3.30*] – ASP97 (*CB, CG*)
	C () [*3.55*] – CYS186 (*SG*)	C () [*3.63*] – ASP97 (*OD1*)

Table 18. Astragalin interaction

Polar	Hydrophobic	pi-pi	cation-pi	Other
O4 (*4*) [*3.75*] – TRP94 (*NE1*)	C10 (*14*) [*3.58*] – TRP94 (*CD1, CG*)	C1 (*5*) [*3.68*] – TRP94 (*CH2, CZ2*)	H1 (*15*) [*3.62*] – HIS113 (*CD2*)	O4 (*4*) [*3.23*] – PHE93 (*CB*)
O3 (*3*) [*3.37*] – ASP97 (*OD1*)	C8 (*12*) [*3.59*] – TRP94 (*CD1, CE2*)	C4 (*8*) [*3.51*] – TRP94 (*CZ2*)	H1 (*15*) [*3.72*] – TYR116 (*CD2, CE2*)	O4 (*4*) [*3.29*] – TRP94 (*CD1, CG*)
O1 (*1*) [*3.74*] – HIS113 (*NE2*)	C7 (*11*) [*3.74*] – TRP94 (*CE2, CZ2*)	C5 (*9*) [*3.05*] – HIS113 (*CD2, CG*)		C8 (*12*) [*3.50*] – TRP94 (*NE1*)
O2 (*2*) [*3.59*] – ARG188 (*CZ, NH1, NH2*)	C10 (*14*) [*3.57*] – TRP102 (*CZ3*)	C6 (*10*) [*3.27*] – HIS113 (*CD2, CG*)		C10 (*14*) [*3.83*] – TRP94 (*NE1*)
H1 (*15*) [*2.99*] – ARG188 (*CZ, NH1, NH2*)	C8 (*12*) [*3.31*] – VAL112 (*CG2*)	C2 (*6*) [*3.51*] – HIS113 (*CD2*)		O3 (*3*) [*3.53*] – ASP97 (*CB, CG*)
O1 (*1*) [*3.18*] – ARG188 (*NH1*)	C10 (*14*) [*3.77*] – VAL112 (*CG2*)	C4 (*8*) [*3.88*] – HIS113 (*CD2*)		O3 (*3*) [*3.62*] – TRP102 (*CZ3*)
		C1 (*5*) [*3.89*] – HIS113 (*CE1*)		O4 (*4*) [*3.34*] – TRP102 (*CH2, CZ3*)
		C6 (*10*) [*3.32*] – TYR116 (*CB, CD2, CG*)		O4 (*4*) [*3.52*] – VAL112 (*CB, CG2*)
		C5 (*9*) [*3.60*] – TYR116 (*CD2*)		O2 (*2*) [*3.26*] – HIS113 (*CD2*)
				C1 (*5*) [*3.86*] – HIS113 (*NE2*)
				C2 (*6*) [*3.27*] – HIS113 (*NE2*)
				C3 (*7*) [*3.51*] – HIS113 (*NE2*)
				C5 (*9*) [*3.36*] – HIS113 (*NE2*)
				C6 (*10*) [*3.71*] – HIS113 (*NE2*)
				C9 (*13*) [*3.81*] – HIS113 (*NE2*)
				O2 (*2*) [*3.12*] – TYR116 (*CD2, CE2, CG*)
				C9 (*13*) [*3.79*] – ASP187 (*OD1*)
				C9 (*13*) [*3.23*] – ARG188 (*NH1*)

Table 19. Beta Sitosterol interaction

Hydrophobic Interactions
C28 [3.56]- ILE215 (*CG2*)
C28 [3.90]- LEU216 (CD2)
C13 ()[*3.15*- TYR219 (*CB, CG*)]
C23 () [3.60]–TYR219 (CD2)
C29() [*3.54*] – TYR219(*CE2*)
C3 ()[3.86]–ILE223 (CG2)
C17()[*3.59*] – ILE223(*CG2*)
C20 ()[3.30]-LEU238(CD2)
C29 ()[*3.48*]–VAL242 (*CB,CG1*)
C9 ()[3.73]-VAL242(CG2)
C26 () [3.01] – ILE245 (CB, CG2)
C24 () [3.45] – ILE245 (CG2)
C25 () [*3.73*] – ILE245 (*CG2*)
C27 () [3.57] – ILE245 (CG2)
C28 () [3.84] – ILE245 (CG2)
C29 () [3.85] – ILE245 (CG2)
C26 () [*3.39*]–LEU246 (*CD2, CG*)
C29 () [3.68] – LEU246 (CG)
C27 () [3.38] – LEU246 (CD2)
C27 () [3.38] – PHE249 (CD2)
C28 ()[3.77]–PHE249 (CD2, CE2)

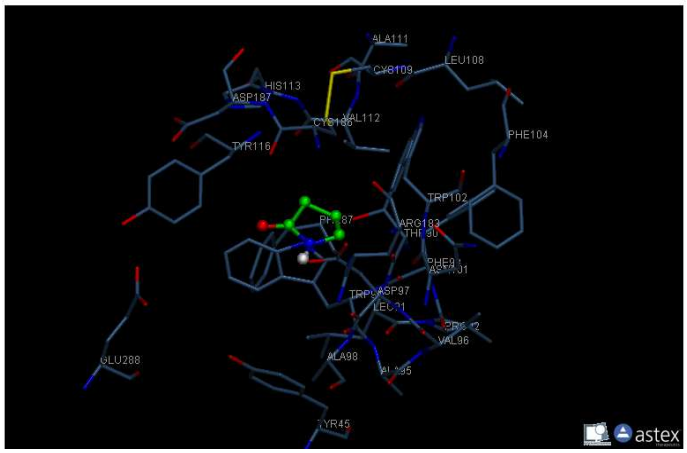

Figure 1. 2-Pyrrolidinone ball and stick model

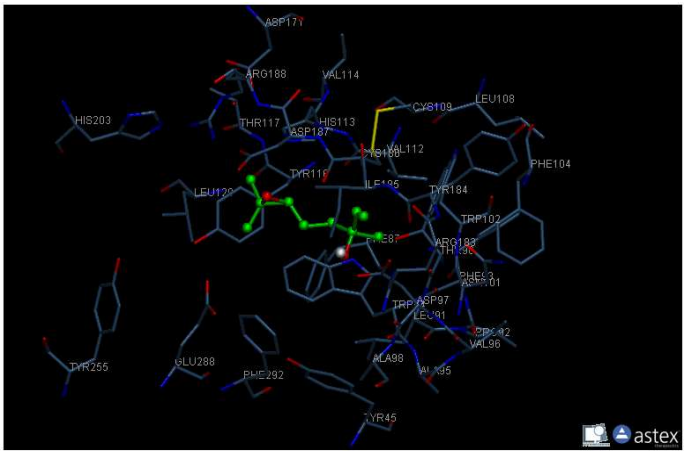

Figure 2. Linalool oxide ball and stick model

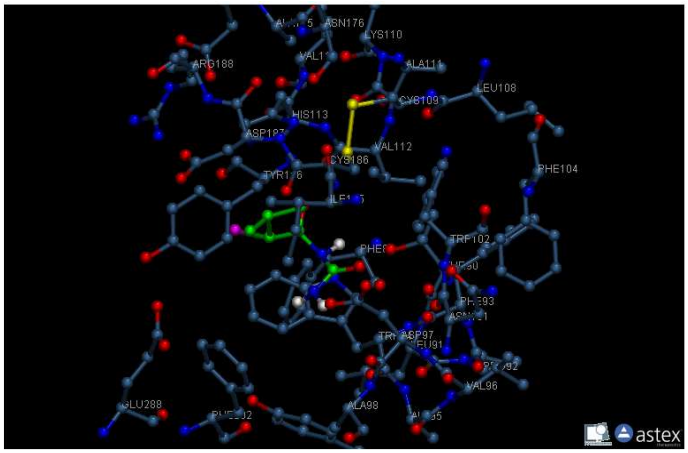

Figure 3. Upiol ball and stick model

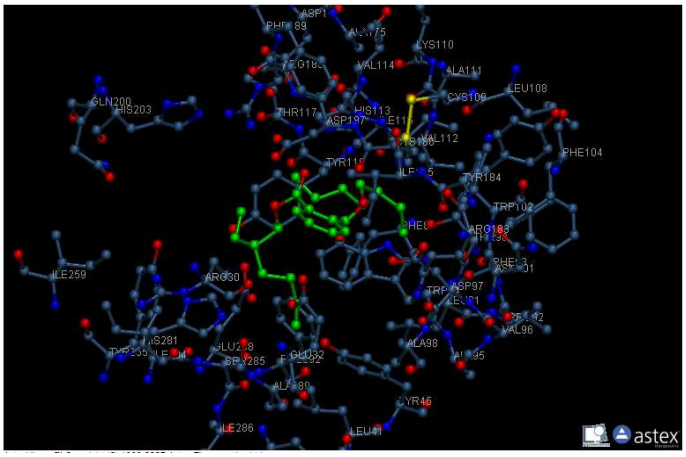

Figure 4. 1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester ball and stick model

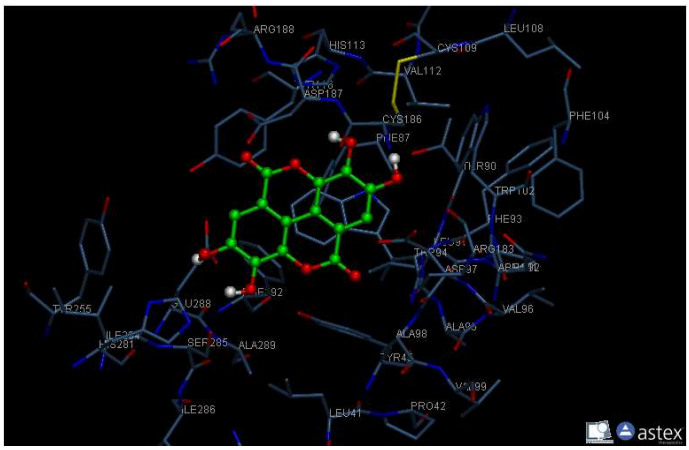

Figure 5. Ellagic acidball and stick model

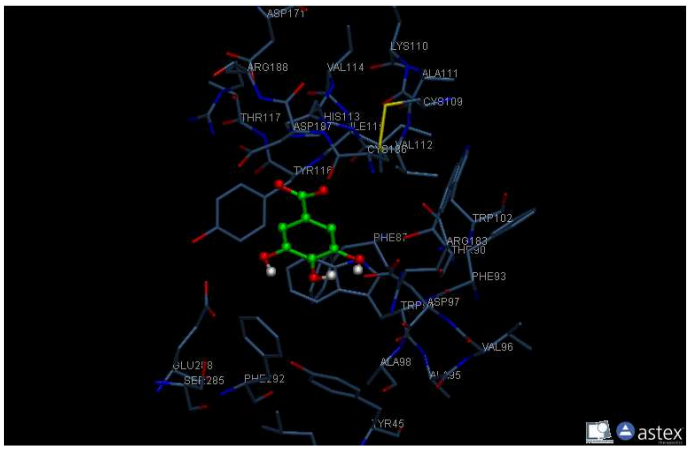

Figure 6. Gallic acid ball and stick model

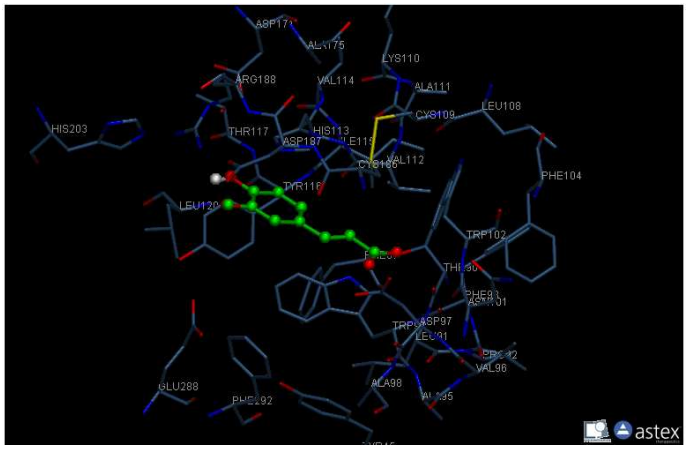

Figure 7. Ferulic acid ball and stick model

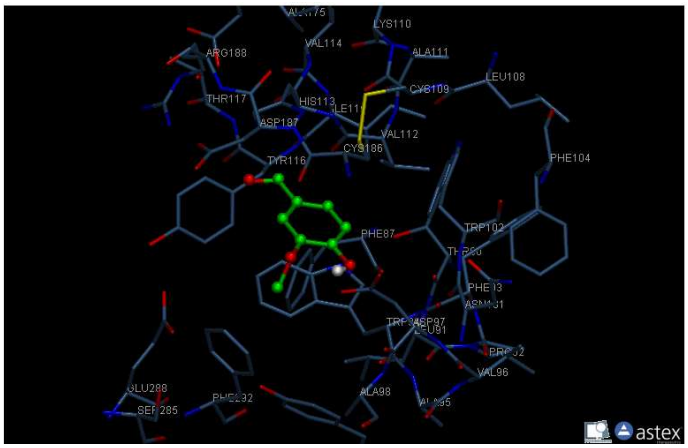

Figure 8. Vanillin ball and stick model

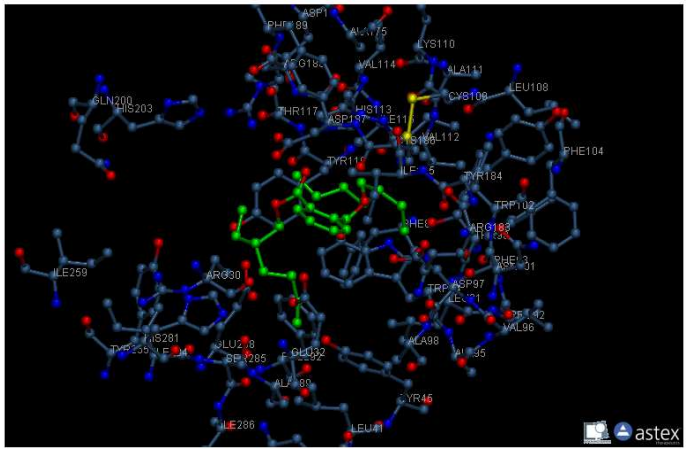

Figure 9. 1,2,3-Cyclopentanetriol ball and stick model

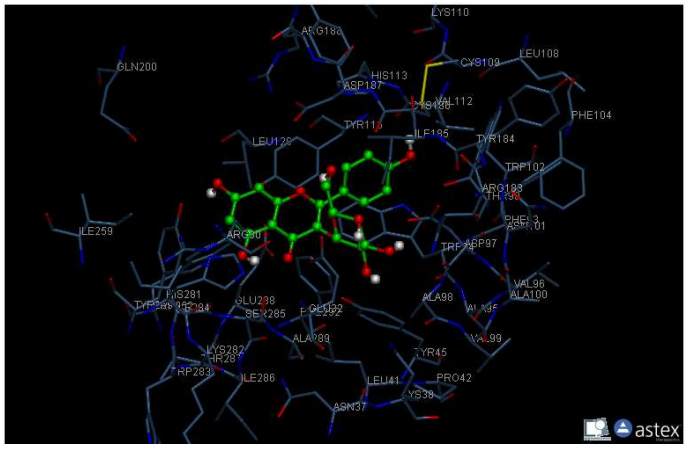

Figure 10. Astragalin ball and stick model

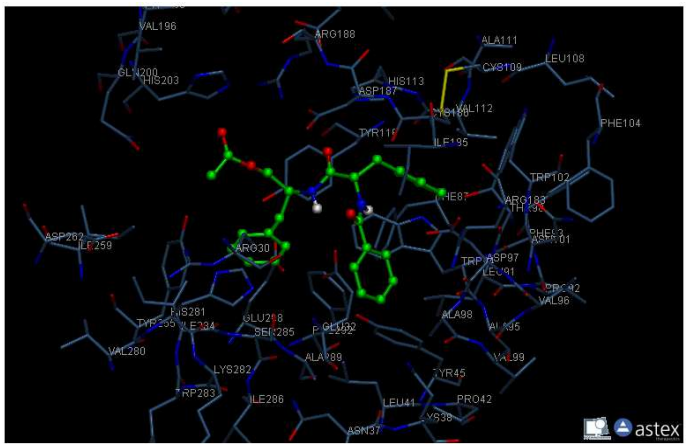

Figure 11. Aurantiamideacetate ball and stick model

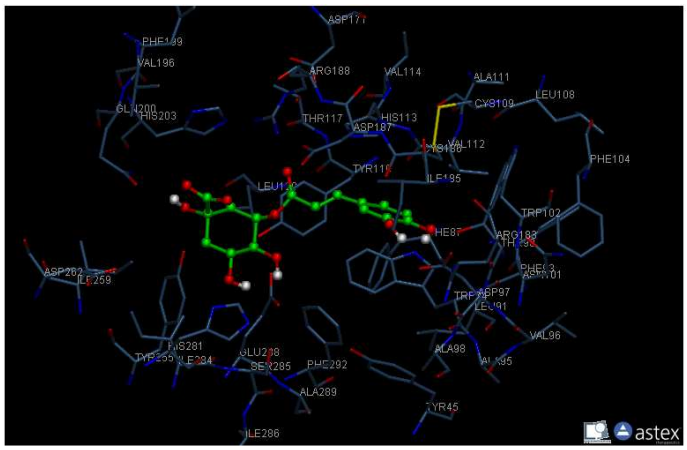

Figure 12. Chlorogenic acid ball and stick model

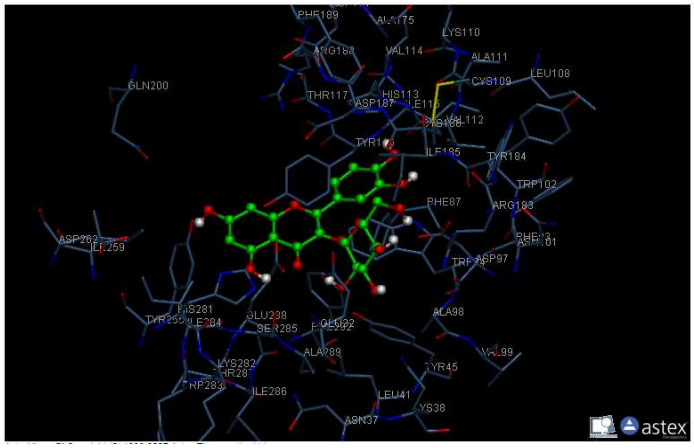

Figure 13. Isoquercetin ball and stick model

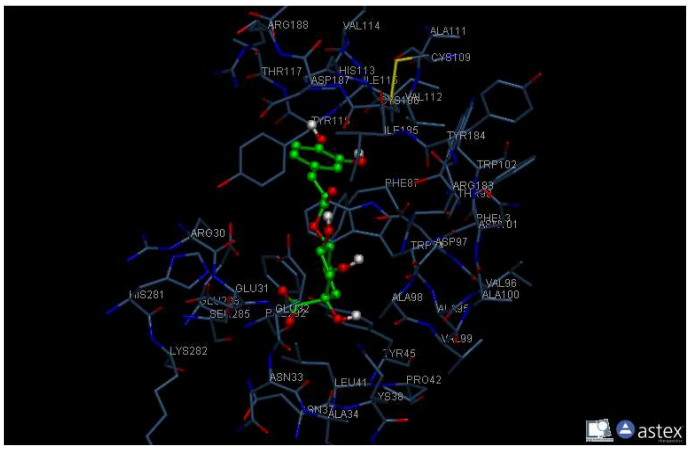

Figure 14. Crypto-chlorogenic acid ball and stick model

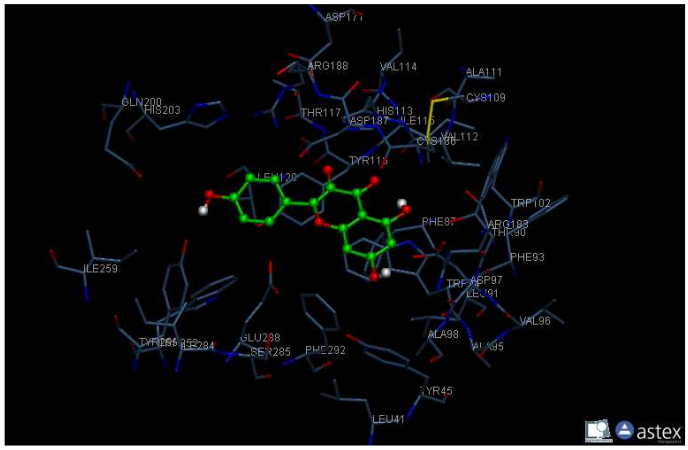

Figure 15. Kaempferol ball and stick model

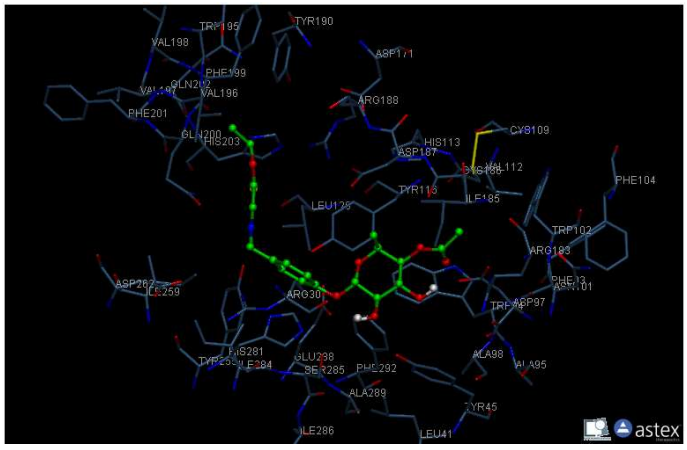

Figure 16. Niaziminin ball and stick model

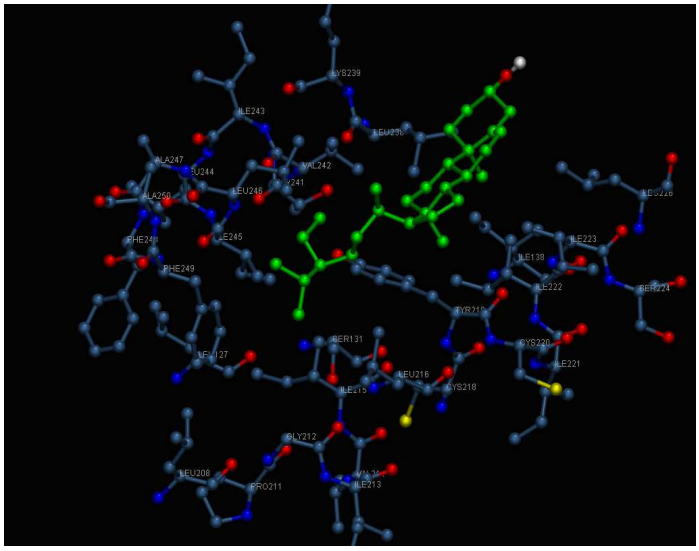

Figure 17. Beta sitosterol ball and stick model

In the present investigation, we found that tryptophan (94) and histidine(113) from the active site of CXCR4 contributed to hydrophobic interaction with Ellagic acid,Aurantiamideacetate. The hydrophobic interactions contributed by CXCR4 when interacting with beta-sitosterol by tyrosine (219), phenylalanine(249) and isoleucine (245). The nature of amino acids present at the active site of receptor are an important to understand interaction studies with ligand. In case of Aurantiamideacetate hydrophobic interactions were contributed by histidine (113) and Isoleucine(284). These amino acids plays crucial role in the docking and non-covalent interaction and defined as the amino acids that can interact with all the selected ligands. Thus these amino acids may play important role in target function of CXCR4.

Moringa oleifera known for its high nutritional and therapeutic potential, only since last two decades serious efforts has been made to explore this plant scientifically. Phytochemical analyses have shown that *M. oleifra* is rich in phenolic acids, flavonoids, alkaloids, phytosterols and glycosides. These phytochemical classes contributing to its diversified pharmacological activities viz. analgesic, anti-inlammatory, antihypertensive, antioxidant, antitumor, antiarthritic, antispasmodic, antiurolithic and hepatoprotective, etc. In the present investigation 16 phytochemicals of *M. oleifera* were docked against CXCR4 receptor. After molecular docking study of selected phytoconstituents and considering their docking score, two compounds viz. ellagic acid and aurantiamide acetate are found to be promising candidate against the CXCR4 receptor. Literature survey has shown that ellagic acid and aurantiamide acetate contribute to diverse pharmacological properties. Ellagic acid (EA) is known to possess multiple biological activities, such as inhibition of proliferation, angiogenesis, oxidation, HIV protease and other processes involved in inflammation and carcinogenesis [20-23]. Whereas, Aurantiamide acetate showed significant anti-inflammatory / antiarthritic and analgesic activity mediated via inhibition of TNF-alpha, IL-2 and other cytokines [24]. *In vitro* and *in vivo* studies demonstrate that aurantiamide acetate may suppress the growth of human malignant gliomas via inhibiting intracellular autophagic flux [25]. From the above references and our research findings, we suggest the possibility of beta sitosterol, ellagic acid and aurantiamide acetate to develop as a CXCR4 antagonist. However, further *in vitro* and *in vivo* studies needed to validate their biological potential.

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REFERENCES

[1] CS Sharma; RK Nema; SN Meyyanathan. *Academic J. Cancer Res.*, **2009**, 2(1), 19-24.
[2] Sharp PM, Hahn BH. Origins of HIV and the AIDS Pandemic. *Cold Spring HarbPerspect Med* **2011**; 1: 1-22.
[3] Bombaywala MA, Hajare RA, Bakde BV, et al. *Int J Pharm Res and Dev*. **2003**,2(1), 1-4.
[4] http://www.who.int/gho/hiv/en/[Last accessed on 2nd June **2015**].
[5] http://naco.gov.in/upload/2014%20mslns/NACO_English%202013-14.pdf[Last accessed on 2nd June **2015**].
[6] Kesarkar R, Sangar VC, Oza G, et al. *Int. J. Pharm. Sci. Rev. Res.* **2014**,26(2),117-122.
[7] Ryan R, Dayaram YK, Schaible D, Coate B, Anderson D. *Current HIV Research*,**2013**, 11,570-575.
[8] Tan Q, Zhu Y, Li J, et al..*Science*,**2013**,341(6152),1387-1390.

[9] Berson JF, Long D, Doranz BJ., Rucker J, Jirik FR, Doms RW. *J. Virology*, **1996**,70, 6288-6295.
[10] Clercq D, *BiochemPharmacol*, **2009**; 77: 1655-1664.
[11] Olson ME, *Syst. Bot*., **2002**, 27, 55-73.
[12] Ramachandran C, Peter KV, Gopalakrishnan PK, *Econ. Bot*,**1980**,34, 276–283.
[13] Aslam M, Anwar F, Nadeem R, et al. *Asian J. Plant Sci*.,**2005**,4,417–421.
[14] Bennett RN, Mellon FA, Foidl N, et al. *J. Agric. Food Chem*.**, 2003**,51,3546–3553.
[15] Amaglo NK, Bennett RN, LoCurto RB, et al. *Food Chem* **2010**,122,1047-1054.
[16] Gowrishankar R, Kumar M, Menon V, et al. *Biol. Trace Elem. Res*., **2010**,133,357-363.
[17] Mbikay M.*Front. Pharmacol*. **2012**,3(24),1-12.
[18] Bikhadi Z, Hazai E. *J. Cheminform*. **2009**,1,1-15.
[19] Solis FJ, Wets RJB.. *Math. oper. Res*.**1981**,6,19-30.
[20] Upgade A, Bhaskar A, Kumarsamy P. *Asian J of biochem*.**2014**,1-11.
[21] Hseu YC, Chou CW, Senthil Kumar KJ, et al.. *Food and Chemical Toxicology* **2012**,50(5),1245-1255.
[22] Bae JY, Choi JS, Kang SW, Lee YJ, Park Y, Kang YH. *Experimental Dermatology* **2010**,19(8),182-190.
[23] Jimenez F, Mitts TF, Liu K, Wang Y, Hinek A. *Journal of Investigative Dermatology* **2006**,126(6),1272-1280.
[24] Nutan MM, Goel T, Das T, et al., *Indian J Med Res* **2013**,137,540-548.
[25] Sashidhara KV, Rosaiah JN, Tyagi E, et al..*Eur J Med Chem* **2009**,44,432-436.
[26] Yang Y, Zhang L, Yang, BX, Tian J, Zhang L. *J. Cell. Mol. Med*. **2015**,19(5),1055-1064.