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In silico evaluation of flavonoids from *Citrus sinensis* as inhibitors of HIV-1 reverse transcriptase

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Abstract
The present study predicts the binding affinities and inhibitory potential of flavonoids from *Citrus sinensis* (sweet orange) against HIV - 1 reverse transcriptase a key enzyme in HIV replication studied computationally using molecular docking. The standard ligand i.e. inhibitor drug molecule 11-cyclopropyl-5,11-dihydro-4-methyl-6h-dipyrido[3,2-b:2',3'-e] [1,4] diazepin-6-one (NVP) act as standard ligand and redock with protein. The redocking score of NVP is compared with the docking score of other ligands obtained from the *Citrus sinensis*.

Keywords: Flavonoids, inhibitors, ligand, evaluation, molecular docking

Introduction
[1] Flavonoids is naturally occurring organic compound exhibit various medicinally important properties. Flavonoids are a large group of naturally occurring phytochemicals known for their medicinal activities like antioxidant**,** anti-inflammatory, and antiviral properties. They become a class of plant secondary metabolites called polyphenols and are widely distributed in fruits, vegetables, tea, wine, and other plant-based foods. Flavonoids are important Phytochemical with numbers of health benefits. [2] They present in a variety of colorful fruits and vegetables. In our diet is the best way to obtain them naturally from fruits. Flavonoids play an important role in variety of biochemical reaction mechanisms in Scavenging reactive oxygen species (ROS), Modulating enzyme function, influencing gene expression, interacting with cellular signaling pathways (e.g., NF-KB, MAPK). The most common sources of flavonoids are fruits like apples, berries, grapes, citrus fruits. Vegetables like onions, kale, broccoli. The drinks like green tea, black tea, red wine, cocoa. Herbs and Spices namely parsley, thyme, peppermint.
[3] An organic compound Nevirapine (NVP) 11-cyclopropyl-5,11-dihydro-4-methyl-6h-dipyrido[3,2-b:2',3'-e] [1, 4] diazepin-6-one having molecular formula $C_{15}H_{14}N_4O$ is an anti-HIV drug, specifically used for HIV-1, and it belongs to the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs). It's typically used along with other antiretroviral drugs to treat [4] HIV infection and AIDS, and also plays a vital role in prohibiting mother-to-child transmission of HIV-1 during birth. Quercetin is a plant pigment (flavonoid). It occurs mainly in many plants and foods, such as red wine, onions, green tea, apples, and berries. Quercetin has antioxidant and anti-inflammatory effects that might help reduce swelling, it kills cancer cells, control blood sugar, and help prevent heart disease.
[5] Molecular docking is a computational technique in which the binding affinity of selected chemical (abbreviated as ligand) studied. [6] The comparative study of standard inhibitor drug molecule with the selected ligand by measuring the docking score glide, Vân der wall interaction hydrogen bonding by using the different software like, auto dock, open Babel, Schrodinger Maestro, Biovia discovery studio, Chem draw, acd lab, polymol etc.Some of them are freely available and some paid version.

Methodology
[6] The five biologically active molecules L1 to L5 taken for the docking study with the standard drug inhibitor molecule. [7] The phytochemicals for this study were obtained online from the Dr duke phytochemical database website of plant extract. The chemical structures of experimental ligands downloaded from the Pub-chem repository.

Ligand selection and preparation: [8] The structure of ligand created in the chem draw software and further interactions studied in Biovia discovery software. The structure of ligands prepared and saved in sdf format for further docking study.

Target Protein Preparation: [9] The high-resolution crystal structure protein of 2.20 Å having RT inhibitor complex in pdb format was retrieved from RCSB protein data bank. The interaction of residue with protein was studied in the Biovia discovery software.

Molecular Docking: [10] Docking study done in the software Schrodinger and compare the binding affinities of flavonoids with known RT inhibitors 11-cyclopropyl-5,11-dihydro-4-methyl-6h-dipyrido[3,2-b:2',3'-e] [1, 4] diazepin-6-one (NVP) as positive controls. The refined experimental ligand L1, L2, L3, L4, and standard inhibitor NVP docked with the protein and docking score observed and put in the form of table.

Table 1: Standard drug &Ligand selected from *Citrus sinensis*

Sr. No.	Label	Ligand	Plant Part
1	NVP	11-cyclopropyl-5,11-dihydro-4-methyl-6h-dipyrido[3,2-b:2',3'-e] [1, 4] diazepin-6-one	Standard Drug isolated from protein obtained from pdb
2	L 1	Hesperidin	Fruit Juice, Flower, Pericarp
3	L 2	Naringin	Fruit Juice, Flower, Pericarp
4	L 3	Quercetin	Fruit Juice, Flower, Pericarp
5	L 4	Rutin	Fruit Juice, Flower, Pericarp
6	L 5	Nobiletin	Fruit Juice, Flower, Pericarp

Results and Discussion

The Ligand L3 shows very high affinity to bind with protein as like to reference drug by the nine amino acid residues namely Leu 100, Lys 101, Lys 103, Val 106, Val 179, Tyr 181, Tyr 188, Leu 234, Tarp 229 as like the inhibitors. The ligand L4 shows the binding affinity with the Pro 95, Lys101, Thr165.The Ligand L4 shows less affinity of binding to the protein and the other ligand L1, L2 and L5 not appear in the docking study and hence its docking score is not visible in software. The various structure of protein with the ligand binding shown below.

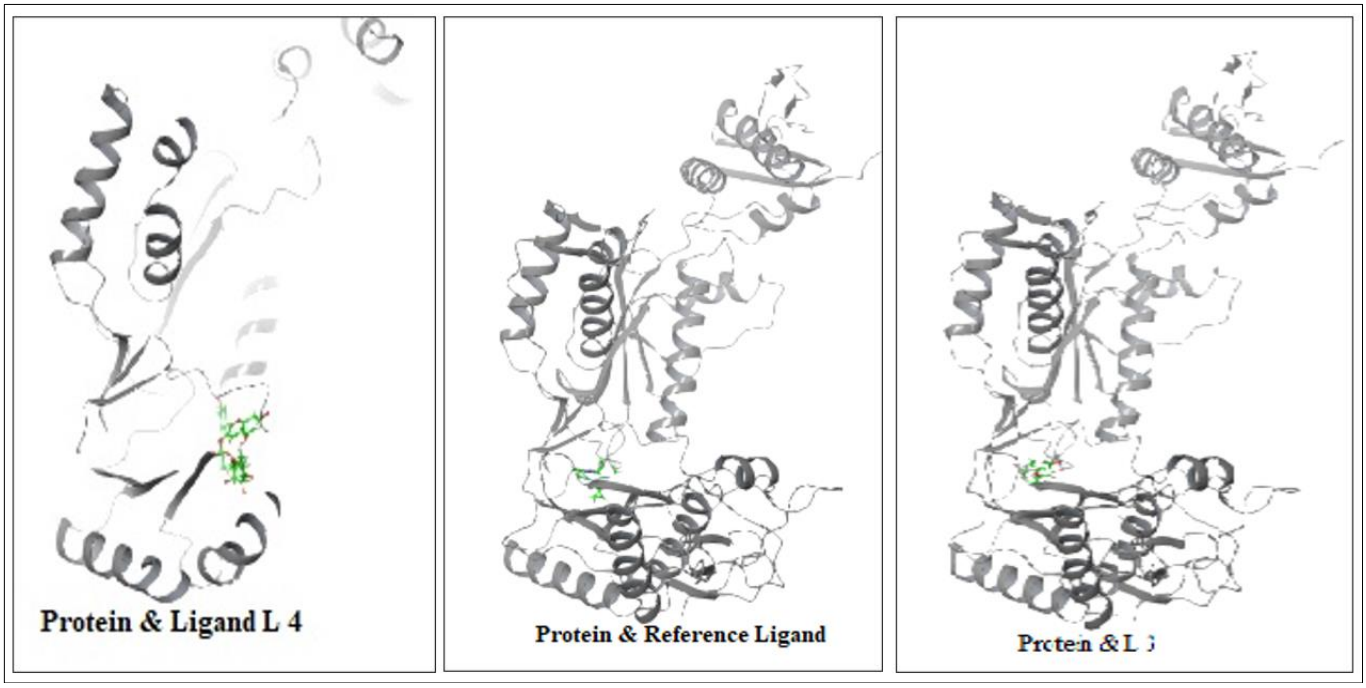


Fig 1: Cartoon structure of protein & Ligands

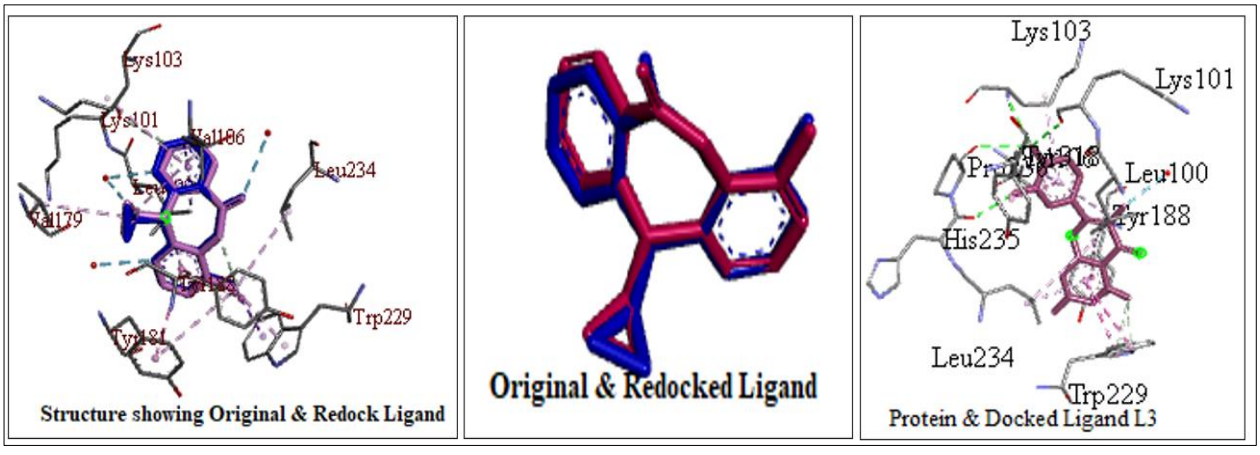
Table: 2 Docking Score of Ligands

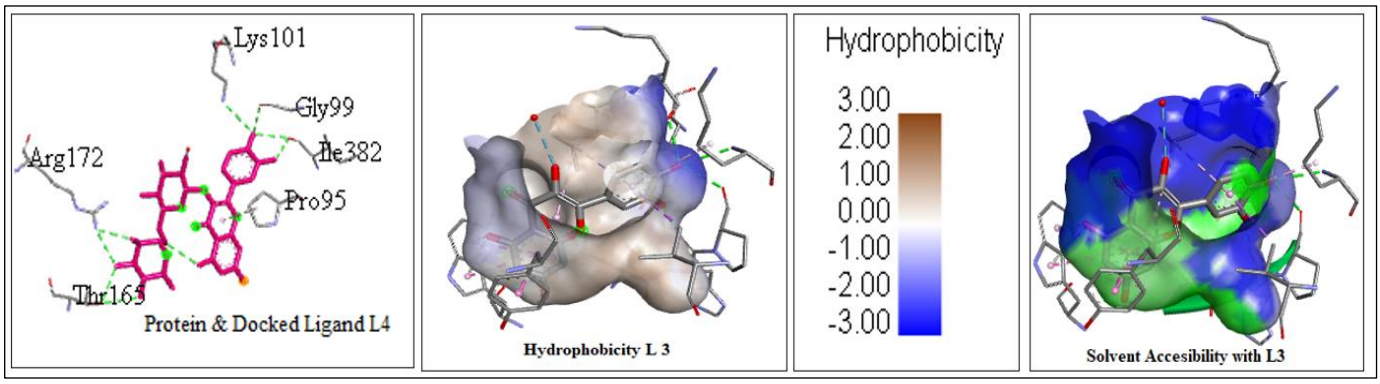
Sr. No.	Ligand	Docking Score	XP G Score	Glide Score	Energy	XP H Bond
1	L 3	-10.511	-10.543	-10.543	13.851	-2.938
2	NVP reference ligand	-9.242	-9.242	-9.242	53.7	-0.597
3	L 3	-8.665	-10.531	-10.531	8.308	-2.949
4	L 4	-5.792	-7.712	-7.712	30.276	-5.19

The observed interaction of most favorable ligands with each residue are discussed here. The ligand L3 shows Very good interaction with residue Leu 100, Lys 101, Lys 103, Val 106, Val 179, Tyr 181, Tyr 188, Leu 234, Tarp 229.

Table 3: Various interactions of Ligands

Sr No	Residue	Ligands	Van der Wall interaction	Coulombic interaction	Distance of residue from ligand	Hydrogen Bonding
1	Leu 100	L3	1.72	0.331	2.544	0
		NVP ligand	2.405	-0.26	2.715	0
		L3	1.719	-0.761	2.5	0
		L4	2.525	-0.545	4.426	0
2	Lys 101	L3	0.468	-3.678	1.72	-1
		NVP ligand	-0.516	-1.359	2.405	0
		L3	0.463	-15.576	1.719	-1
		L4	-1.176	-22.925	2.525	0
3	Lys 103	L3	1.635	0.609	1.9	-0.072
		NVP ligand	-2.27	-1.024	2.212	0
		L3	1.768	-12.958	1.882	-0.072
		L4	-0.046	-11.977	7.187	0
4	Val 106	L3	-2.688	0.062	2.691	0
		NVP ligand	-3.72	-0.233	2.406	0
		L3	-2.715	-0.557	2.699	0
		L4	-0.019	-0.3	10.239	0
5	Val 179	L3	-0.518	-0.124	3.896	0
		NVP ligand	-2.197	0.134	2.346	0
		L3	-0.525	0.084	3.882	0
		L4	-0.56	-0.433	3.399	0
6	Tyr 181	L3	-0.625	0.671	2.313	0
		NVP ligand	-4.039	-0.538	2.515	0
		L3	1.887	1.155	2.19	0
		L4	-3.48	-3.483	2.334	0
7	Tyr 188	L3	-1.998	-1.553	2.423	-0.141
		NVP	-5.449	-0.828	2.371	0
		L3	-3.477	2.051	2.803	0
		L4	-0.161	-0.117	7.036	0
8	Tarp 229	L3	7.512	-1.36	1.688	0
		NVP	-2.546	-0.342	2.704	0
		L3	0.178	-0.262	2.112	0
		L4	-0.159	-0.543	6.895	0
9	Leu 234	L3	-3.148	0.443	2.483	0
		NVP	-3.255	0.207	2.361	0
		L3	-0.423	-0.287	2.32	0
		L4	-0.023	-0.225	10.349	0





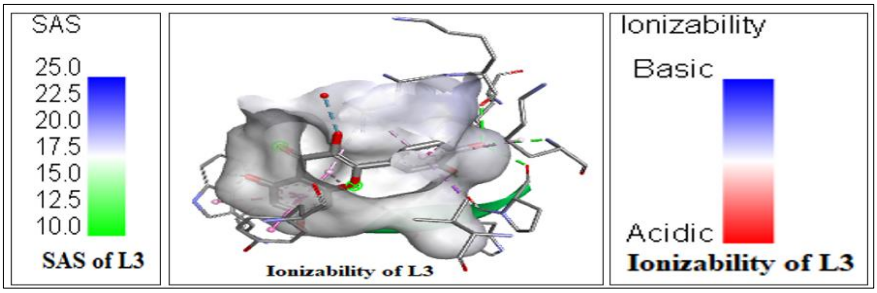


Fig 2: Structure showing binding of docked ligand affinity.

Conclusion

The flavonoids from *Citrus sinensis* namely Quercetin labelled as L3 in experiment shows strong binding affinity with protein HIV - 1 VRT through the residue Leu 100, Lys 101, Lys 103, Val 106, Val 179, Tyr 181, Tyr 188, Leu 234, Tarp 229. It shows similar docking score as that of the standard drug molecule hence it can be considered for further potential antiviral development.

Conflict of Interest

Author has not any conflict of interest.

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