

A NOVEL APPROACH FOR RATIONALE SELECTION OF MEDICINAL PLANTS AGAINST VIRUSES VIA MOLECULAR DOCKING STUDIES

Siva Ganesh M, Preeti Awasthi, Ajay Kumar Timiri and Manik Ghosh*

Department of Pharmaceutical Sciences & Technology, Birla Institute of Technology,

Mesra, Ranchi-835215-Jharkhand, India

Email: manik@bitmesra.ac.in

Abstract: Discovery of drugs against viruses is always an attractive area of research. Plants are important natural source for discovery of drugs against viruses. Here in this article we targeted at two points. First the selection of a particular plant against viruses can be done more rationally by using the latest computer techniques i.e. docking studies of the known phytochemicals on various viral protein targets. Second with help of literature search and docking studies we identified some important natural compounds that can be used as natural leads. For this, we selected important phytoconstituents from 20 plants for docking studies using Maestro (Glide) and Lead IT (FlexX). Later those phytochemicals which got good docking scores were further docked in Autodock 4.2 in order to find out the estimated inhibition constant. Flavonoids, curcumin and other compounds gave good docking scores and better inhibition constant. These compounds can be used as natural leads and analogues and derivatives can be synthesized to get effective antiviral agents. In addition this approach gives a way to avoid random selection of plant for a particular activity, in order to save time, chemicals and effort of the medicinal chemist.

Keywords: Viruses, Docking, Phytochemicals, Maestro, Lead IT, Autodock

1. Introduction

Plants having different biosynthetic pathways are great sources of natural compounds, which can be used for various therapeutic purposes.¹ More than 100 compounds acting as anticancer and anti-infective agents, at different stages of clinical development are derived from natural sources.² Viral infections cause diseases having huge risk like Acquired Immunodeficiency Syndrome (AIDS), Dengue fever, Chikungunya fever and common flu etc. Many plants can be used as a source of antiviral agents; different compounds are having broad-spectrum activity. With the increase in separation techniques and screening methods, medicinal plants promise as good sources of antiviral agents.

The main aim of a medicinal chemist is to get active extracts, fractions or compounds against a

particular target. In the recent times, computational chemistry has become an economic solution for drug discovery and identify of lead molecules. This when coupled with natural products makes a medicinal chemist to explore more efficiently with less work.³ In this attempt we initially docked various phytochemicals present in different plants selected from ayurvedic literature. To our expectation, some natural compounds like curcumin, quercetin etc. which gave good docking scores was already reported as potential antiviral agents. In other case, the plants containing these HITs were found to have reported antiviral activities. This supports our method of using computational chemistry for better selection of plants against viruses. Further, we were successful in bringing out some of the major natural leads that can be used as antiviral agents.

In order to estimate the biological activities of various chemical constituents of twenty different plants, docking was done on Maestro (Glide) and Lead IT (FlexX). Chemical moieties that got good docking scores were further docked in Autodock in order to estimate the inhibition constant. The main objective behind these docking studies is to suggest the use of docking studies in selection of plants against viruses. Secondly, here we identified some natural leads that were proved to be potential antiviral agents, based on docking studies and literature search. Analogues and derivatives can be synthesized to get effective antiviral agents. An attempt has also been made to compare docking studies with the co-crystallized molecules. A brief introduction on the life cycle of viruses selected is given in order to have a better understanding of various drug targets for the reader.

2. Viral Life Cycles and Important Drug Targets

2.1 Influenza

Influenza viruses are a group of RNA viruses that causes common flu. There are mainly two types of Influenza virus, A and B. Virus is mostly spherical having lipid bilayer. It consists of spike like projections on surface of lipid bilayer which are made up of Haemagglutinin (HA) and Neuramidase (NA). HA is synthesized from HA0 which is made of HA1 and HA2, linked by disulphide bonds. HA1 which is the globular part helps in binding with the sialic acid receptors. HA2 is fibrous stem, called as fusion peptide, which activates the fusion of viral envelope and host cell membrane. Neuramidase has enzymatic activity which helps in the breakage of sialic acid and glycoproteins. Virus enters the host cell by receptor mediated endocytosis. Low pH in endosome causes conformational changes,

releasing vRNP into cytoplasm. Crm dependent pathway helps in moving vRNA into nucleus, viral transcription and translation occurs in the nucleus.

Influenza virus has negative stranded RNA (having 8 segments code for 11 proteins). For the purpose of transcription, first it has to be converted into positive stranded RNA. RNA dependent RNA polymerase can start the replication without primer. The genome of virus encodes for 11 proteins. Segment 7 codes for matrix 1 (M1) and matrix 2 (M2), segment 8 codes non structural protein 1 (NS1) and nuclear export protein (NEP). M2 and NEP are present in less amounts as they are sliced products. Negative sense vRNA are to be exported out of the nucleus and this is done by Crm1 dependent pathway via nuclear pores. Nucleoprotein interacts with Crm1 in which there is no GTP hydrolysis. Recently it was found that nucleoprotein moves towards the upper side of the infected nuclei because of polarization. Influenza uses the plasma membrane of the host cell for formation of viral particles and migrate to the neighboring host cells and these viral particles had double lipid layer. Viruses protrude out from apical side and so HA, NA and M2 move towards the apical side. M2 tail is important for viral formation. M1 is present under lipid bilayer and is important for budding of new viruses. Before leaving the virus has to cleave from sialic acid residues from glycoproteins and this can be done with the NA.⁴

2.2 Dengue

Dengue fever caused by Dengue virus (DENV 1-4) is a mosquito borne disease. Dengue virus belongs to the family *Flaviviridae* with four different serotypes (DENV 1-4) causes dengue fever and dengue hemorrhagic fever.

DENV is positive stranded RNA virus. Initially the virus enters the cell by receptor mediated endocytosis and decrease in pH releases nucleocapsid into the cytoplasm. The capsid is dispersed and viral RNA moves to the rough endoplasmic reticulum (RER), where it codes for the polyprotein by attaching itself to ribosome. This polyprotein will breakdown into structural and non-structural proteins with the help of viral protease enzyme. The structural proteins include capsid protein, premembrane protein and envelope protein. The non-structural proteins include NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5. The capsid protein orients towards the cytoplasmic side of RER envelope protein and premembrane protein towards the lumen side of RER. Once the translation is complete and folding of proteins occurs, the NS proteins stimulate the synthesis of new RNA. This RNA is then capped by capsid protein and will get formed into nucleocapsid. Then it enters the lumen side where it is further enveloped with premembrane protein and envelope protein. This immature virions then pass through the golgi apparatus where they mature and can cause infection, are released from the cell.⁵

2.3 Human Immunodeficiency Virus (HIV)

Human Immuno Deficiency virus simply called HIV causes Acquired Immunodeficiency Syndrome (AIDS). HIV is a retrovirus, viruses having the RNA but get converted to DNA in the host cell.

The first step is the attachment of the virus to the T-cell surface. This can be achieved by two proteins namely gp120 and gp41 which attach to the CD4 and CCR5/CXCR4 receptors. gp120 is actually made of three sugar coated proteins which when virus comes in contact with host cell, the three

proteins are dissolved exposing gp41. gp41 binds to chemokine receptor, which makes the viral envelope and host membrane to fuse together. This releases viral genetic material into the host cell. Then viral RNA is converted into double stranded DNA by a process referred to as reverse transcription assisted by enzyme reverse transcriptase. HIV uses nucleotides of host to achieve this reverse transcription. Then this newly formed DNA will move through the nuclear membrane and gets integrated with host's DNA by the help of enzyme integrase. The viral DNA now called provirus. The viral DNA synthesizes two strands of RNA, one strand synthesizes the requirements of virus like reverse transcriptase, integrase and structural proteins etc. Other strand synthesizes genetic material of virus. Once the proteins are synthesized, they must be broken down into individual proteins and this can be achieved by protease enzyme. This is followed by aggregation of various HIV components to form new virus. The newly formed virions move themselves outside the host cell called as budding.⁶

2.4 Chikungunya

Chikungunya is a class of Arbovirus. It enters the host cell by endocytosis. The decrease in pH causes conformation changes in envelope protein, exposing E1 peptide. This peptide helps in fusing viral membrane with host membrane. This releases viral genome into the cytoplasm. Translation of viral mRNA leads to formation of two precursors of non structural proteins and cleavage of these proteins leads to formation of NSP1-NSP4. NSP1 along with NSP2 is involved in catalyzing the synthesis of negative strand of RNA and have RNA capping properties, NSP2 shows RNA helicase, RNA phosphatase and protease activity, NSP3 has

replication property and NSP4 has polymerase activity. These proteins together forms a viral replication complex which synthesizes a negative RNA strand intermediate and this acts as an template for synthesis of genomic (49S) and subgenomic (26S) RNA. Subgenomic RNA carries out translation and

drives expression of C-pE2-6K-E1 which on processing by autoprotease and signalase release Capsid (C), pE2 and E1 glycoprotein. Binding of viral nucleocapsid and viral RNA promotes viral assembly which leads to budding at cell membrane, which transforms into mature virions.⁷

3. Methods of virtual screening:

3.1 Maestro: The computation studies were carried using Maestro 8.5.

Lig prep:

The chemical constituents were obtained from literature search. The possible states of drawn structures were prepared between the pH of 7 to 2.0 using Epik. Desalt was done and all tautomers were generated. All the possible stereoisomers were generated at a maximum of 32 per ligand.

Protein preparation:

The preprocessing was done. Bond orders were assigned, addition of hydrogens and deletion of waters was performed. Then the heterostates of the ligands if present were generated. H-bonding was optimized. OPLS2001 is used for energy minimization.

Receptor grid generation:

Receptor grid generation is done with default values. In co-crystallized proteins, ligand was picked for centroid and active site residues were selected in proteins which are not co-crystallized (2FOM and 3TRK).

Ligand docking:

Glide is used for docking natural compounds into the protein molecules. The molecules were docked using standard precision. Residues interaction scores were taken within 12 Å range.

The following proteins (Table 1) were used as drug targets downloaded from Protein Data Bank.

Table 1. Different drug targets in different viruses

Viral Protein	Influenza	Dengue	HIV	Chikungunya
Protease		2FOM	1ODY	3TRK
Methyl transferase		2P40		
Reverse transcriptase			2RF2	
Neuramidase	1L7F			

All the proteins were downloaded from Protein Data Bank (www.rcsb.org)

The chemical constituents from the following plants (Table 2) were used for docking studies.

Table 2. Different phytochemicals from plants docked

Sl. No.	Plant	Chemical constituents docked
1	<i>Curcuma longa</i> ⁸	Curcumin (1), demethoxycurcumin (2), β -phellandrene (3), p-cymene (4), α -turmerone (5)
2	<i>Ficus religiosa</i> ⁹	Kaempferol (6), myricetin (7), quercetin (8), methyl oleanolate (9), β -sitosterol (10), stigmasterol (11), lanosterol (12)
3	<i>Cuminum cyminum</i> ¹⁰	Cuminaldehyde (13), limonene (14), α -pinene (15), β -pinene (16), o-cymene (17), α -terpinene (18), γ -terpinene (19), safranal (20), linalool (21)
4	<i>Punica granatum</i> ¹¹	Citric acid (22), mallic acid (23), gallic acid (24), catechin (25), quercetin (8), α -tocopherol (26), linoleic acid (27), oleic acid (28), β -sitosterol (10)
5	<i>Oroxylum indicum</i> ¹²	Baicalein (29), oroxyline (30), pinostrobin (31), stigmast-7-en-3-ol (32)
6	<i>Mangifera indica</i> ¹³	Mangiferin (33), protocatechuic acid (34), catechin (25), shikimic acid (35), mangostin (36), gallic acid (24), ethyl gallate (37)
7	<i>Achyranthes aspera</i> ¹⁴	D-Glucuronic acid (38), oleanolic acid (39), achyranthine (40), ecdysterone (41)
8	<i>Barleria prionitis</i> ¹⁵	Barlerinoside (42), barlerin (43)
9	<i>Terminalia chebula</i> ¹⁶	gallic acid (24), chebulanin (44), chebulinic acid (45)
10	<i>Pterocarpus marsupium</i> ¹⁷	kinotannic acid (46), pterocarpol (47), liquiritigenin (48), gallic acid (24)
11	<i>Cajanus cajan</i> ¹⁸	Cajanin (49), pinostrobin (50), longistylin A (51), cajanuslactone (52), vitexin (53)
12	<i>Acacia nilotica</i> ¹⁹	Gallic acid (24), Apigenin (54), protocatechuic acid (34), rutin (55)
13	<i>Zingiber officinale</i> ²⁰	Curcumene (56), fernesene (57), gingerene (58)
14	<i>Piper longum</i> ²¹	Piperine (59), asarinine (60), sesamin (61), caryophyllene (62), gingerene (63), p-cymene (4)
15	<i>Euphorbia hirta</i> ²²	Quercetin (8), myricetin (7), rutin (55), kaempferol (6), gallic acid (24), protocatechuic acid (34)
16	<i>Cissus quadrangularis</i> ²³	Ascorbic acid (64), β -sitosterol (10), quercetin (8), amyryn (65)
17	<i>Ocimum sanctum</i> ²⁴	Eugenol (66), ursolic acid (67), carvacrol (68), linalool (21), caryophyllene (62), estragole (69)
18	<i>Tabernaemontana divaricata</i> ²⁵	Conophylline (70), Dregarnine (71), tabermontanine (72)
19	<i>Hibiscus sabdariffa</i> ²⁶	Hibiscitrin (73), β -sitosterol (10), citric acid (22), delphinidin-3-glucoside (74), protocatechuic acid (34), quercetin (8)
20	<i>Allium sativum</i> ²⁷	Allixin (75), propiin (76)

* The numbers in the brackets implies the structure number in supplementary file.

3.2 Lead IT

The ligands prepared in Maestro 8.5 were used for docking. They were saved in .sdf format and used for docking studies.

Protein preparation:

Particular chains having the receptor were selected as receptor components. Then reference ligand is selected if present, else specified by selecting specific amino acids. All the chemical

ambiguities, which are crystallographically unresolved structures were resolved and receptor was confirmed.

Then the docking is done using default parameters using hybrid approach, followed by visualization using Pose View.

3.3 Autodock:

Proteins prepared in Maestro saved in .pdb format were converted to Autodock compatible atom type using OpenBabel. Ligands were prepared in Maestro and saved in .pdb format. These were converted into Autodock compatible atom type using OpenBabel.

Grid parameter file (.gpf) and drug parameter file (.dpf) were generated using MGL Tools-1.4.6. Receptor grids were generated by picking up an atom in active site using 60 x 60 x 60

points in X, Y and Z directions with grid spacing of 0.375Ao. Later docking was done using Autodock 4.2 with the following parameters. Runs: 50, population size: 150, number of evaluations: 2500000 and generations: 27000.

4. Results and discussion:

Flavonoids gave good docking scores and inhibition constant values. Apart from flavonoids, gallic acid gave good docking score against Dengue, Chikungunya and HIV proteins. The docking scores of HITs were tabulated (Table 3 & 4). The inhibition constants of HITs were estimated using Autodock 4.2 and was tabulated (Table 5), following Maestro and FlexX docking scores.

Table 3. Docking scores of co-crystallized molecules with their respective proteins

Viral Protein	Co-crystallized molecule	Maestro	Lead IT	Autodock
Methyl transferase of dengue (2P40)	7MeGpppG	-7.812	-23.436	17.02 mM
Protease of HIV (1ODY)	LP-130	-8.319	ND	37.83μM
Reverse transcriptase of HIV (2RF2)	7e	-8.206	ND	ND
Neuramidase of influenza (1L7F)	BCX-1812	-8.288	-28.635	149.05μM

*ND- Not docked

Table 4. Maestro scores of HITs

Sl. No.	Chemical constituent	1L7F	2FOM	2P40	3TRK	1ODY	2RF2
1.	Kaemferol	-4.893	-5.240	-6.299	-6.819	-5.920	-8.117
2.	Myricetin	-5.340	-5.574	-6.337	-5.564	-6.210	-8.107
3.	Quercetin	-5.270	-4.551	-6.357	-5.992	-7.050	-7.742
4.	Gallic acid	-4.611	-6.084	-6.408	-6.153	-6.243	-7.116
5.	β -sitosterol	-4.771	-4.499	-3.893	-3.781	-4.130	-4.381
6.	Achyranthine	-5.777	-5.421	-5.021	-5.755	-6.091	-8.360
7.	Linalool	-9.430	-0.622	-5.527	-2.730	-6.905	-6.880
8.	Delphinidin	-6.172	-5.886	-5.991	-6.364	-7.130	-7.558
9.	Piperine	-4.264	-4.138	-4.655	-6.451	-6.261	-3.821
10.	Mangiferin	-6.210	-5.360	-5.720	-5.210	-7.740	-3.520

Table 5. FlexX scores of HITs

Sl No	Chemical constituent	1L7F	2FOM	2P40	3TRK	1ODY	2RF2
1.	Curcumin	-22.870	-9.567	-19.068	ND	-33.973	ND
2.	Gallic acid	-39.539	-7.961	-25.987	ND	19.090	-14.954
3.	Achyranthine	-43.696	-6.543	-17.903	-6.312	-19.764	-10.988
4.	Mallic acid	-43.417	-4.598	-16.308	-0.511	-22.396	-12.338
5.	Citric acid	-46.410	-2.359	-17.156	2.398	-25.051	-10.473
6.	Quercetin	-22.455	-10.339	-19.899	ND	-24.165	-21.230
7.	Cajanin	-20.545	-12.245	-14.063	4.863	-23.821	-14.063
8.	Kaemferol	-20.468	-10.282	-17.644	ND	-25.031	-19.561
9.	Myricetin	-19.520	-9.556	-18.992	ND	-25.756	-19.052
10.	β -sitosterol	ND	-6.0841	-3.040	ND	ND	-21.130

2FOM-Dengue protease, 2P40-Methy transferase of Dengue, 3TRK-Chikungunya protease, 1ODY-HIV protease, 2RF2-HIV Reverse transcriptase, 1L7F-Neuramidase of Influenza

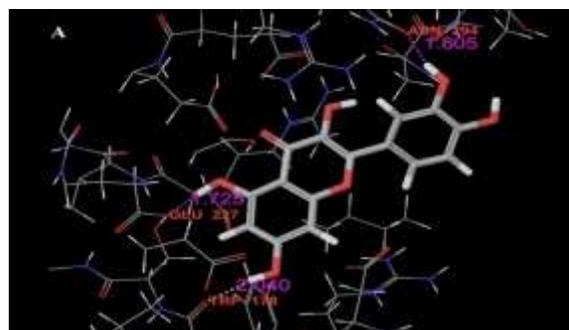
Table 6. Autodock scores (Inhibition constant)

SI No	Chemical constituent	1L7F	2FOM	2P40	3TRK	1ODY	2RF2
1.	Kaemferol	4.35 μ M	12.30 μ M	62.22 μ M	2.39 μ M	42.20 μ M	86.21 μ M
2.	Myrecetin	1.79 μ M	5.85 μ M	64.43 μ M	847.42nM	105.90 μ M	11.00 μ M
3.	Quercetin	2.83 μ M	6.64 μ M	124.80 μ M	2.68 μ M	47.67 μ M	74.45 μ M
4.	Gallic acid	100.10 μ M	176.80 μ M	23.86 μ M	377.00 μ M	4.10 μ M	180.50 μ M
5.	Curcumin	38.90 μ M	89.79 μ M	3.00mM	72.45 μ M	468.70 μ M	27.66 μ M
6.	Achyranthine	1.78mM	457.60 μ M	135.81 μ M	2.65mM	7.30mM	1.55mM
7.	Mangiferin	25.42 μ M	1.23 μ M	50.14 μ M	21.53 μ M	29.41 μ M	21.73 μ M
8.	Shagoal	125.95 μ M	87.30 μ M	311.45 μ M	40.51 μ M	1.50mM	52.84 μ M
9.	Linalool	333.43 μ M	779.80 μ M	1.79mM	413.90 μ M	4.67mM	577.75 μ M
10.	Delphinidin	9.78 μ M	31.49 μ M	27.19 μ M	26.33 μ M	210.74 μ M	220.74 μ M

2FOM-Dengue protease, 2P40-Methy transferase of Dengue, 3TRK-Chikungunya protease, 1ODY-HIV protease, 2RF2-HIV Reverse transcriptase, 1L7F-Neuramidase of Influenza

Quercetin and Kaemferol, which are flavonoids gave good docking scores against most of the viral proteins. In Maestro, quercetin interacted well with Neuramidase of Influenza (1L7F) and it gave a docking score of -7.742. It made interactions with three residues. With Glu 227, the hydrogen bond length was 1.72 Å, with Asn 294, it is 1.81 Å and with Trp 178, it is 2.04 Å (Fig. 1). The same compound was docked with methyl transferase of dengue (2P40) in Maestro gave docking score of 6.36. It made four interactions, Ser150 having H-bond length 1.84 Å, Lys14 having H-bond length 2.04 Å, Leu20 having H-bond lengths 2.08 Å, 1.79 Å, and Asn18 having H-bond length 1.84 Å (Fig. 2). In Lead IT, kaemferol made five interactions with 1L7F giving docking score of -20.468. The hydrogen bonding lengths were 2.34 Å with Arg 371, 1.52 Å with Arg 118, 2.02 Å with Asp 151, 1.86 Å with Trp

178 and 2.13 Å with Asn 347 (Fig. 3). In Autodock, Kaemferol made two interactions with 1L7F, one with Ile 427 having H-bond length 1.88 Å and other with Ile 149 having H-bond length 1.99 Å, The estimated inhibition constant value was found to be 4.35 μ M (Fig. 4). Quercetin made three interactions with 1L7F in Autodock, with Arg 371 having H-bond length 1.99 Å, with Ser 404 having H-bond length 2.16Å and with Asp 151 having H-bond length 1.99 Å. The estimated inhibition constant was found to be 2.83 μ M.



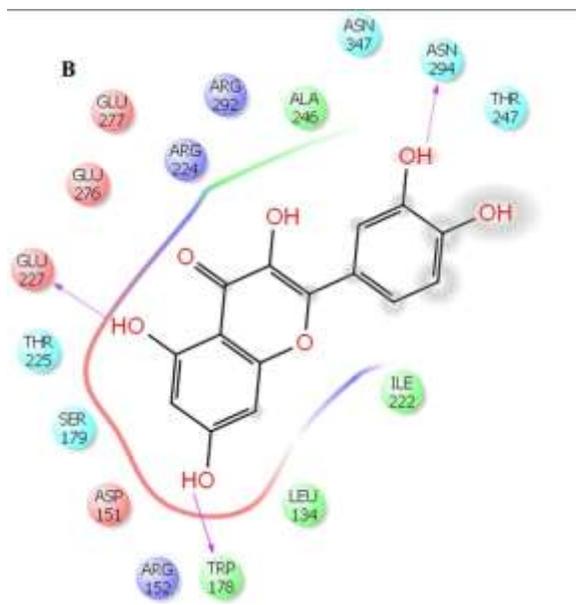


Fig. (1): Maestro: (A) Interaction of Quercetin with IL7F with a docking score -7.742 interacting with Glu 227 (H-bond length 1.72 Å) Asn 294 (H-bond length 1.81 Å), Trp178 (H-bond length: 2.04 Å) (B) Interactions in ligand interaction viewer

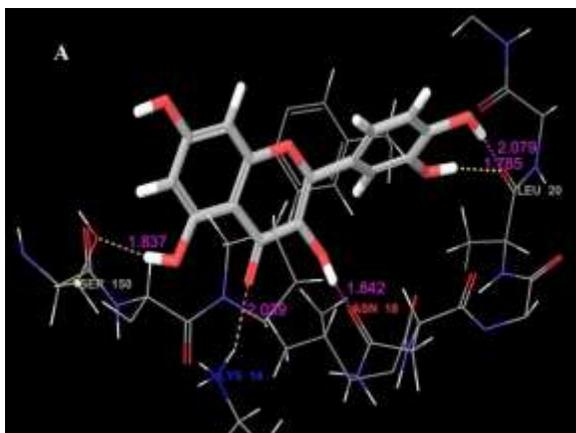


Fig. (2): Maestro: (A) Interaction of Quercetin with 2P40 interacting with docking score -6.36 interacting with Ser150 (H-bond length 1.84 Å), Lys14 (H-bond length 2.04 Å), Leu20 (H-bond lengths 2.08 Å, 1.79 Å), and Asn18 (H-bond length: 1.84 Å) (B) Interactions in ligand interaction viewer

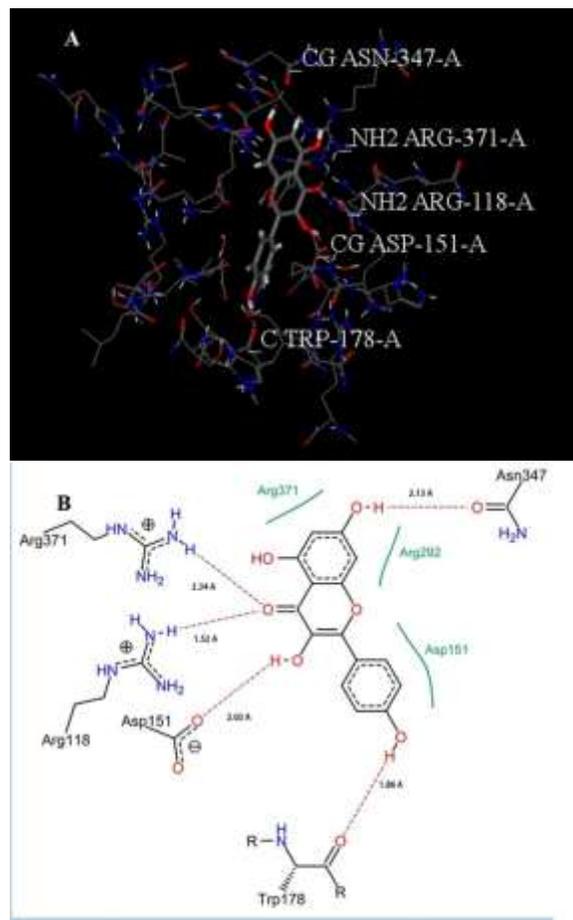


Fig. (3): Lead IT: (A) Interaction of Kaemferol with IL7F with a docking score of -20.468 interacting with Arg 371 (H-bond length 2.34 Å), Arg 118 (H-bond length 1.52 Å), Asp 151 (H-bond length 2.02 Å), Trp 178 (H-bond length 1.86 Å) and Asn 347 (H-bond length: 2.13 Å) (B) Display of interactions in pose viewer

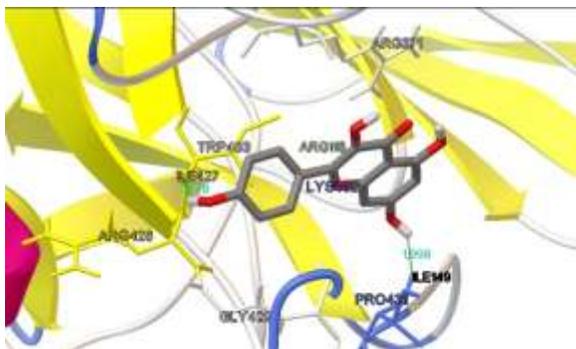


Fig. (4): Interaction of Kaempferol with 1L7F in Autodock interacting with Ile 427 (H-bond length 1.88 Å) and Ile 149 (H-bond length 1.99 Å)

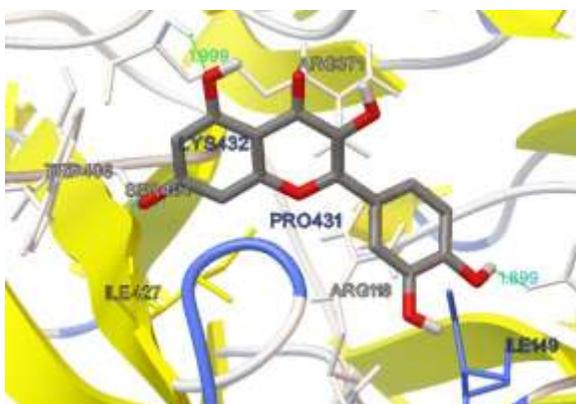


Fig. (5): Interaction of Quercetin with 1L7F in Autodock interacting with Arg 371 (H-bond length 1.99 Å), Ser 404 (H-bond length 2.16 Å) and Asp 151 (H-bond length 1.89 Å)

Flavonoids gave excellent docking scores and inhibition constant values. Apart from flavonoids, gallic acid gave good docking score values against Dengue, Chikungunya and HIV proteins.

Chemical constituents of *Euphorbia hirta* gave good docking scores on dengue, HIV and influenza proteins. Agnes gyuris *et al.* (2009) has established anti-HIV properties of *Euphorbia hirta*. They found that the aqueous and methanolic extracts containing the polyphenolic compounds were found to have anti-HIV properties and non-polar extracts

were found to be inactive.²⁸ In another study it was found that flavonoids act against HIV by acting on reverse transcriptase and integrase enzymes.²⁹ Docking studies on these proteins found to be good. Another study indicated quercetin to be a potential agent against dengue virus and *Euphorbia hirta* was found to be effective against dengue virus.^{30, 31} *Ficus religiosa* fruits which are rich in flavonoids are believed to be good source of antiviral agents.

Curcumin, an active ingredient in *Curcuma longa* is proved to have potential antiviral properties against HIV.³² The same compound gave good docking scores against HIV proteins like reverse transcriptase and protease. Gingerols and shagoals are the active constituents of *Zingiber officinale* gave good docking scores on proteins selected. The same plant was proved to be potential agent against influenza.³³

Pundaleekappa (2012) has discovered anti-HIV properties of *Ocimum sanctum*. They found linalool as one of the component of extract having the anti-HIV properties.³⁴ Mangiferin and gallic acid are the main components of *Mangifera indica*, gave good docking studies on almost all the viruses. Mangiferin is reported to antagonize cytopathic effects of HIV gave good docking studies against HIV protease. The same compound was reported to have potential activity against HIV protease.³⁵ In another study gallic acid which gave excellent docking scores on HIV reverse transcriptase and found to have inhibitory activity on the same.³⁶

Dengue and chikungunya are viruses of contemporary time and based on the above studies, docking protocol can help for rationale selection of natural compounds and plants against these viruses.

5. Conclusion:

Flavonoids are found to be good antiviral agents and *Euphorbia hirta*, which is rich in flavonoids is found to be a potential agent against HIV and dengue virus. Other plants like *Cissus quadrangularis* and fruits of *Ficus religiosa* which are rich sources of flavonoids can also act as antiviral agents. Curcumin, an important phytoconstituent of *Curcuma longa* has given good docking scores, also found to be a potential antiviral agent. Gallic acid which is a main component of many plants have good docking interactions is also found to be potential antiviral agent. *Ocimum sanctum* is another plant whose chemical constituents gave good docking

scores, proved to have potential antiviral activity. Chemical constituents from other plants like *Zingiber officinale* and *Achyranthes aspera* are also expected to have potential antiviral activity among the plants considered. By this attempt we can prove, use of computational chemistry is a reliable method for the better selection of plants against viruses.

In addition, flavonoids, curcumin, gallic acid, linalool and chemical constituents from *Zingiber officinale* and *Achyranthes aspera* can be used as natural leads based on docking studies and literature search. Their analogues and semi-synthetic derivatives can be synthesized to get effective antiviral agents in the future.

6. References

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