Journal of Applied Biology & Biotechnology Vol. 9(S1), pp. 40-51, September, 2021
Available online at http://www.jabonline.in
DOI: 10.7324/JABB.2021.95.1s7

Ab-initio modelling and docking evaluation of geographically derived coat proteins of chilli leaf curl virus with flavonoids and chemical compounds

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ARTICLE INFO

Article history:
Received on: February 05, 2021
Accepted on: April 14, 2021
Available online: September 20,2021

Key words:
Coat protein AV1, flavonoids, molecular docking, plant virus, chilli leaf curl virus

ABSTRACT

Chilli leaf curl virus (ChiLCV) belongs to the genus begomovirus (Family Geminiviridae), can infect chilli and many other crops. The coat protein (CP) of ChiLCV binds with the genomic viral ssDNA and shuttles it in and out of the cell nucleus. The distinct role of CP genes is viral capsid formation and transmission by whitefly. In this study, the interaction of CP with selected plant flavonoids and chemical compounds is explained. The CP of ChiLCV were selected from India, Pakistan, Oman, and Sri Lanka. This study focuses on understanding the structure of CPs from different regions and molecular docking studies to inhibit ssDNA binding for transportation of CP AV1 of ChiLCV. Molecular docking is carried between proteins and selected flavonoids and chemical compounds. Flavonoids show potent inhibition at the binding site of AV1. The outcomes obtained from this study direct that flavonoids' performance promises as compare with other chemical compounds. This information might be interesting to study plant defense mechanisms based on the plants' unique compounds.

1. INTRODUCTION

Chilli leaf curl virus (ChiLCV) is a destructive virus among chilli varieties worldwide [1]. This viral infection causes a significant economic crisis in the market [2]. The characteristic symptoms are curly leaves, blistered interveins, and stunted growth. *Polyphagotarsonemus latus* (Mites), *Scirtothrips dorsalis* (thrips), and *Bemisia tabaci* (whitefly) are the active vectors of ChiLCV [3]. Chattopadhyay *et al*. [4] found the infectivity by a complex consisting of monopartite, ChiLCV, and a DNA-beta satellite. Tomato leaf curl Bangladesh beta satellite acts as the factor of chilli leaf curl disease (ChiLCVD). George *et al*. [5] identified bipartite and monopartite begomovirus association with alpha and beta satellites in ChiLCVD. The satellite, DNA β, is often associated with the DNA A genome [4]. The right promoter viral strand transcribed the DNA A that codes for coat protein (CP) and pre-coat protein. In contrast, the left promoter transcribed the replication initiator protein (C1), transcriptional activator protein (C2), replication enhancer proteins (C3), and C4 protein complementary strand of the sense strand. The pathogenesis and acquired symptoms are due to the single protein βC1 encoded by satellite DNA β [6].

Besides, CP is prominent in the vector specificity and viral capsid formation, and vector-mediated transmission [7]. The extermination of viruses or pathogens in the chilli is still challenging due to the limited resources and approaches. By determining the presence of CP in the chilli plant, we can assure the infection of ChiLCV in the host plant. CP plays a significant role in the virus's attachment and the accumulation of ssDNA into it. Many viral resistance plant studies used CP as the primary source [8].

Structure associated drug design and virtual molecular library screening are highly dependent on the protein structure prediction. 3D structure development was less and a deficit in the area of protein large databases. The three-dimensional models of unknown proteins can be developed by using homology modeling with template protein configurations. Those modeling aiding us in examining the binding loci and drugs suits those binding sites of protein [9]. We are representing four viral proteins from the different geographical areas for which pathological features are

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well studied. This structural prediction emphasizes the in-depth knowledge of virus infection's molecular mechanism [10].

As per the modeller structures, we have to select the inhibitors to block the specific protein's functionality. The natural compounds are preferred over the chemical compounds. The comparison is necessary, and the *in silico* approach is a productive way to sort out the numerous inhibitors against the viral factor. Natural compounds such as flavonoids are broadly validated in most viral studies [11]. Flavonoids are well known for their antimicrobial activity, and they are the typical components present in almost all plants. The *Solanaceae* family constitutes different flavonoids, such as kaemferol, quercetin, catechin, and epicatechin are predominant [12]. Six chemical inhibitors such as isoproterenol, riboflavin, atropine, albendazole, neomycin, and ampicillin were evaluated for the tobacco mosaic virus infection, *Solanaceae* family [13]. Here, we compared the natural flavonoids and chemical inhibitors to shortlist the best active ligand against ChiLCV infection.

Nowadays, it has become easy to guess the molecule binding orientation of drugs, even it was small, and affinity can be calculated [14]. In this study, we carried out the homology modelling for all four coat proteins of ChiLCV from India, Oman, Pakistan, and Sri Lanka. We performed molecular docking against the chemical compound and natural flavonoids using modelling and docking software. Growing *in silico* studies benefits *in vitro* studies, such as drug designing, primer designing, and gene silencing [10].

2. MATERIALS AND METHODS

2.1. Sequence Retrieval and ORF Finding

Protein sequences for ChiLCV of different geographical areas such as India, Oman, Pakistan, and Sri Lanka were retrieved from the GenBank. Specific CP sequence from the whole genome was identified using an ORF finder, and their physicochemical composition was analyzed using ProtPram software. Clustal Omega was used to compare and find the similarity of the sequences with Multiple sequence alignment.

2.2. Homology Modeling of the Coat Protein

Ab initio 3D models were prepared through the software Phyre 2. From the obtained models, the best was selected from each protein were energy minimized by the YASARA tool. The predicted models are evaluated by the structural analysis and verification server, Molprobity. The Ramachandran plot validates the developed models through the software Molprobity. The models were selected and could be used for further analysis based on the percentage of favor amino acid and outliers' frequency. Active sites of the validated models were predicted using Discover Visualizer studio.

2.3. Docking with Chemical Compounds and Flavonoids

2.3.1. Compound screening

A total of 14 ligands, including 6 chemical compounds and 8 flavonoids, were obtained from the previous studies. All six compounds were efficient with the notable characters of oral assimilation and absorption of the intestinal epithelium. ADME (Adsorption, Distribution, Metabolism, and Excretion) properties were calculated using SwissADME.

Molecular docking is a key tool to predict protein-ligand interaction. For docking calculations, the PyRx software package with Autodock Vina was employed (https://pyrx.sourceforge.io/). The ligand molecules' structures were downloaded from PubChem and chebi (http://www.ebi.ac.uk/chebi/) in .sdf format and converted to .pdb format using Discover Visualizer studio, which is recognized by PyRx and Autodock Vina. Both selected files of protein and ligands were fed as macromolecules and ligands to PyRx, respectively. The protein and ligand hydrogen were immediately applied using the PyRx hydrogen (H) repair feature. Consequently, the Discovery Studio Visualizer (D.S.V.) will produce a two-dimensional (2D) ligand and target interaction structure.

3. RESULTS AND DISCUSSION

3.1. Sequence Retrieval and Physiochemical Parameters

The retrieved nucleotide sequence of CP was translated into protein sequence through smart blast in the ORF finder were shown in Table 1. In the secondary structure prediction, the different amino acids present in the CP gene of ChiLCV with physiological and chemical parameters. The molecular weight, number of amino acids, and theoretical pI values were listed in Table 2. The CP multiple sequence alignment shows that sequences share high similarity and all the conserved regions are the same (Fig. 1).

3.2. Ab-initio Modelling of Coat Protein and Validation of the 3D Model

A 3D model of the ChiLCV CP from Oman, India, Sri Lanka, and Pakistan were created in the present research. The model was developed using the *ab initio* homology modelling via the Phyre 2 server (Fig. 2). The validation of all four coat proteins performed by the Ramachandran plot was shown in Figure 3. The characteristics of the models were listed in Table 2.

3.3. Lipinski Rule and ADME Prediction

Significant properties of ADME like water solubility, level of human oral absorption in GI, Blood-Brain barrier permanent level,

Table 1: Retrieved sequence accession no and Protein ID.

Virus name	Accession no	Protein name	Protein accession no
Chilli leaf curl virus isolate CapAS 2, complete genome	KM023148.1	Coat protein	AIR77200.1
Chilli leaf curl virus clone Wat-122, complete genome	KX787939.2	Coat protein	APC65287.2
Chilli leaf curl virus complete genome, clone RM270	LN886652.1	Coat protein	CUR29891.1
Chilli leaf curl virus isolate CL-15 from Sri Lanka, complete genome	JN555600.1	Coat protein	AEY77827.1

Table 2: Physiological and chemical analysis of predicted coat protein of ChiLCV from different geographical areas.

Physiological and chemical parameters	Value	Geographical area
Number of amino acids	257	Oman
Molecular weight	29,714.19	
Theoretical pI	10.12	
Total number of negatively charged residues (Asp + Glu)	21	
Total number of positively charged residues (Arg + Lys)	44	
Number of amino acids	256	India
Molecular weight	29,664.22	
Theoretical pI	10.06	
Total number of negatively charged residues (Asp + Glu)	21	
Total number of positively charged residues (Arg + Lys)	44	
Number of amino acids	256	Sri Lanka
Molecular weight	29,581.26	
Theoretical pI	9.99	
Total number of negatively charged residues (Asp + Glu)	21	
Total number of positively charged residues (Arg + Lys)	44	
Number of amino acids	256	Pakistan
Molecular weight	29,687.15	
Theoretical pI	10.08	
Total number of negatively charged residues (Asp + Glu)	22	
Total number of positively charged residues (Arg + Lys)	44	

a)

b)

c)

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CLUSTAL O(1.2.4) multiple sequence alignment

ALQ43532.1:1-256          MSKRPTDIIISTPASKVRRRLNFDSPYASRAAVPTVRVIKARAWANRPMNRKPRMYRMYR   60
AIC83088.1:1-256          MSKRPADIIISTPASKVRRRLNFDSPYASRAAAPTVRVTKARAWVNRPMNRKPRMYRMYR   60
CUR29891.1:1-256          MSKRPADIIISTPASKVRRRLNFDSPYASRAAAPTVRVTKARAWVNRPMNRKPRMYRMYR   60
YP_005352657.1:1-256      MSKRPADIIISTPASKVRRRLNLDSPYASRAAAPIVRVTKARAWANRPMNRKPRMYRMYR   60
CAM33228.1:1-256          MSKRPADIIISTPASKVRRRLNFDSPYASRAAAPIVRVTKARAWANRPMNRKPRMYRMYR   60
                          *****:***************:*********.** *** ***** .**************

ALQ43532.1:1-256          SPDVPRGCEGPCKVQSFESRHDVVHIGKVMCISDVTRGTGLTHRVGKRFCVKSVYVLGKI   120
AIC83088.1:1-256          GPDVPRGCPWPCKVQSFESRHDVVHIGKVMCISDVTRGTGLTHRVGKRFCVKSVYVLGKI   120
CUR29891.1:1-256          SPDVPRGCEGPCKVQSFESRHDVVHIGKVMCISDVTRGTGLTHRVGKRFCVKSVYVLGKI   120
YP_005352657.1:1-256      SPDVPRGCEGPCKVQSFESRHDVVHIGKVMCISDVTRGTGLTHRVGRRFCVKSVYVLGKI   120
CAM33228.1:1-256          SPDVPRGCEGPCKVQSFESRHDVVHIGKVMCISDVTRGTGLTHRVGKRFRVKSVYVLGKI   120
                          .*******  ************************************:** **********

ALQ43532.1:1-256          WMDENIKTKNHTNSVMFFLVRDRRPVDKPQDFGEVFNMFDNEPSTATVKNLHRDRYQVLR   180
AIC83088.1:1-256          WMDENIKTKNHTNSVMFFLVRDRRPVDKPQDFGEVFNMFDNEPSTATVKNMHRDRYQVLR   180
CUR29891.1:1-256          WMDENIKTKNHTNSVMFFLVRDRRPVDKPQDFGEVFNMFDNEPSTATVKNMHRDRYQVLR   180
YP_005352657.1:1-256      WMDENIKTKNHTNSVMFFLVRDRRPVDKPQDFGEVFNMFDNEPSTATVKNMHRDRYQVLR   180
CAM33228.1:1-256          WMDENIKTKNHTNSVMFFLVRDRRPVDKPQDFGEVFNMFDNEPSTATVKNMHRDRYQVLR   180
                          ************************************************:*********

ALQ43532.1:1-256          KWHATVTGGQYASKEQALVKKFVRVNNYVVYNQQEAGKYENHTENALMLYMACTHASNPV   240
AIC83088.1:1-256          KWHATVTGGQYASKEQALVKKFVRVNNYVVFNQQEAGKYENHTENALMLYMACTHASNPV   240
CUR29891.1:1-256          KWHATVTGGQYASKEQALVKKFVRVNNYVVDNQQEAGKYENHTENALMLYMAWTHASNPV   240
YP_005352657.1:1-256      KWHATVTGGQYASKEQALVKKFVRVNNYVVYNQQEAGKYENHTENALMLYMACTHASNPV   240
CAM33228.1:1-256          KWHATVTGGQYASKEQALVKKFVRVNNYVVYNQQEAGKYENHTENALMLYMACTHASNPV   240
                          ******************************** ********************* *******

ALQ43532.1:1-256          YATLKIRIYFYDSVSN      256
AIC83088.1:1-256          YATLKIRIYFYDSVSN      256
CUR29891.1:1-256          YATLKIRIYFYDSVSN      256
YP_005352657.1:1-256      YATLKIRIYFYDSVSN      256
CAM33228.1:1-256          YATLKIRIYFYDSVSN      256
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d)

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CLUSTAL O(1.2.4) multiple sequence alignment

NP_808823.1:1-256         MSKRPADMIISGPVSKYRRLLSSISPYSKRAAVRIVRATKGKEWANRPMNRKPMFYRMYR   60
AEY77827.1:1-256          MSKRPADMIISGPVSKYRRLLTSTSPYSKRAAVRIVRATKGKEWANRPMNRKPMFYRMYR   60
AEY77833.1:1-256          MSKRPADMIISGPASKYRRLLTSTSPYSRRAAVRIVRATKGKEWANRPMNRKPMFYRMYR   60
                          ************.*******:* ****:*********************************

NP_808823.1:1-256         SPDVPKGCEGPCKVQSFESRHDVVHIGKVMCISDVTRGTGLTHRIGKRFCAKSVYVLGKI   120
AEY77827.1:1-256          SPDVPRGCEGPCKVQSFESRHDVVHIGKVMCISDVTRGTGLTHRVGKRFCVKSVYVLGKI   120
AEY77833.1:1-256          SPDVPKGCEGPCKVQSFESRHDVVHIGKVMCISDVTRGTGLTHRVGKRFCVKSVYVLGKI   120
                          *****:*******************************************:****** *********

NP_808823.1:1-256         WMDENIKTKNHTNSVMFFLVRDRRPVDKPQDFGDVFNMFDNEPSTATVKNMHRDRYQVLR   180
AEY77827.1:1-256          WMDENIKTKNHTNSVMFFLVRDRRPVDKPQDFGDVFNMFDNEPSTATVKNMHRDRYQVLR   180
AEY77833.1:1-256          WMDENIKTKNHTNSVMFFLVRDRRPVDKPQDFGDVFNMFDNEPSTATVKNMHRDRYQVLR   180
                          ************************************************************

NP_808823.1:1-256         KWHATVTGGQYASKEQALVKKFVRVNNYVVYNQQEAGKYENHSENALMLYMACTHASNPV   240
AEY77827.1:1-256          KWHATVTGGQYASKEQALVKKFVRVNNYVVYNQQEAGKYENHSENALMLYMACTHASNPV   240
AEY77833.1:1-256          KWHATVTGGQYASKEQALVKKFVRVNNYVVYNQQEAGKYENHSENALMLYMACTHASNPV   240
                          ************************************************************

NP_808823.1:1-256         YATLKIRIYFYDSVTN 256
AEY77827.1:1-256          YATLKIRIYFYDSVTN 256
AEY77833.1:1-256          YATLKIRIYFYDSVTN 256
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Figure 1: Multiple sequence alignment of retrieved coat protein sequences with other protein sequences a) India b) Oman c) Pakistan d) Sri Lanka.

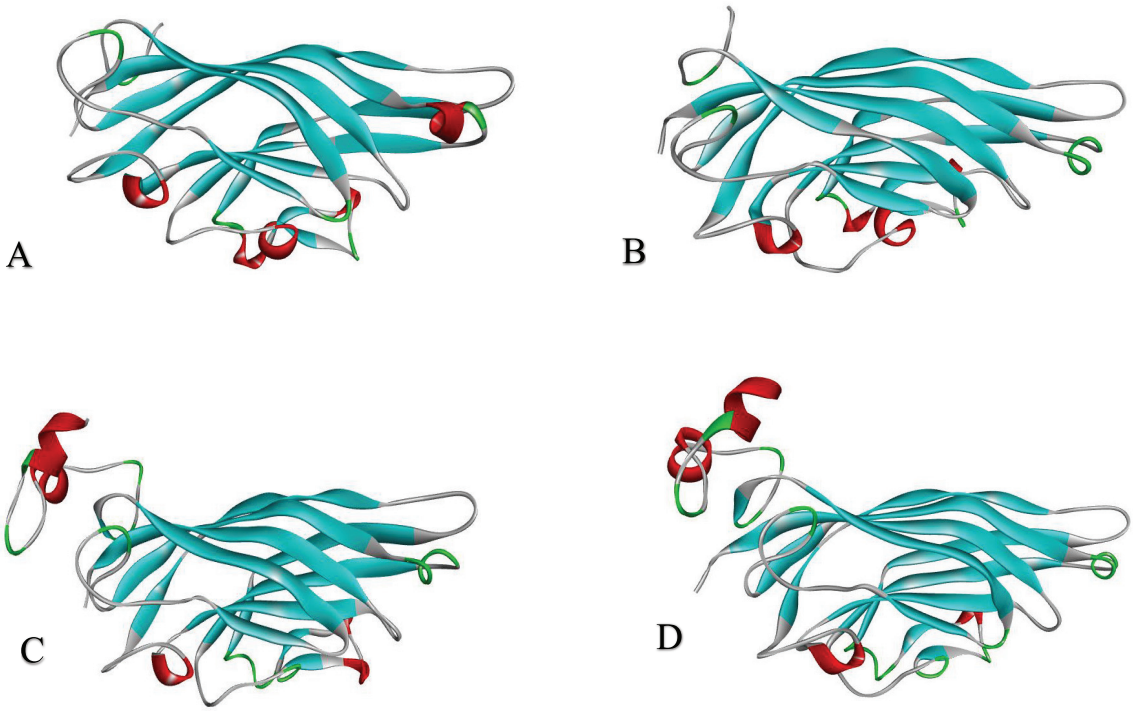


Figure 2: *Ab initio* modeling of coat proteins. a) India, b) Oman, c) Pakistan, and d) Sri Lanka.

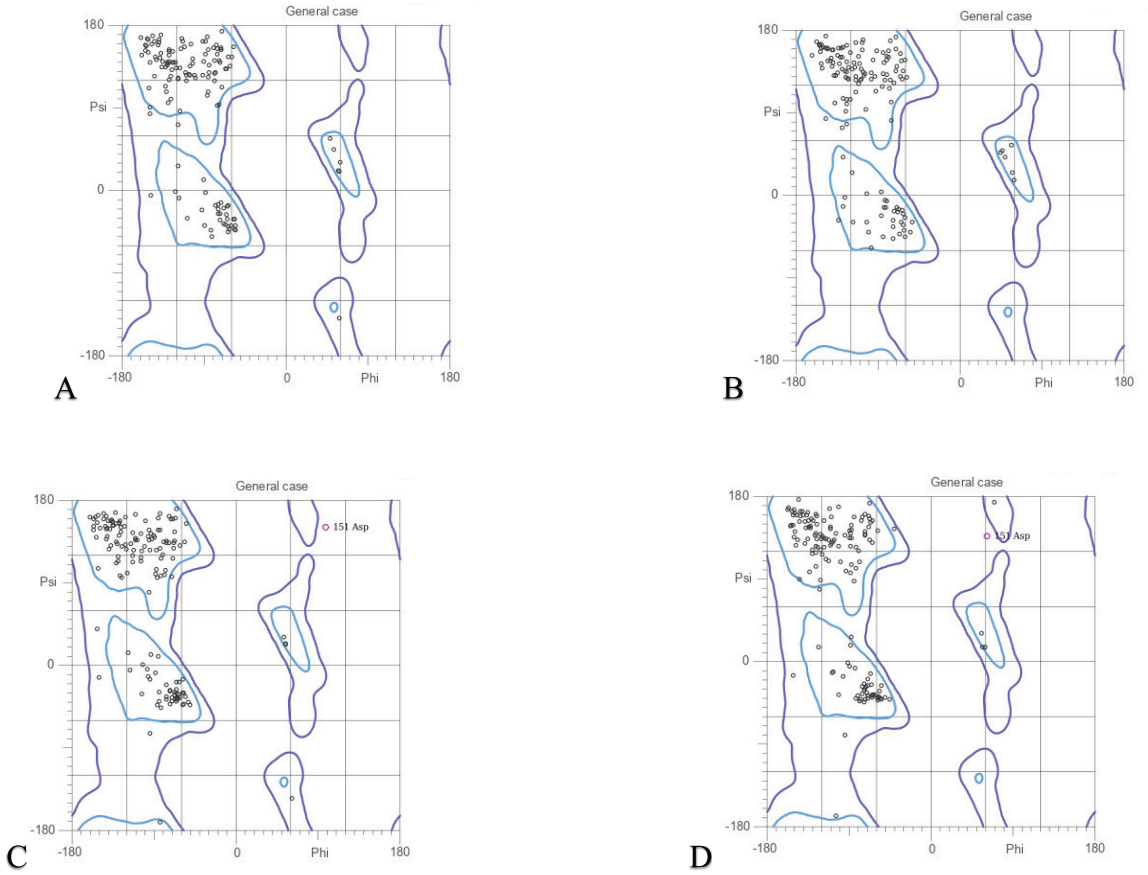


Figure 3: Ramachandran plot obtained using Molprobity. a) India, b) Oman, c) Pakistan, and d) Sri Lanka.

Table 3: Structure validation scores using Molprobity server for the coat protein of ChiLCV.

S. No	Parameters	India	Oman	Pakistan	Sri Lanka
1	No. of residues in favored region	186 (96.37%)	188 (96.91%)	206 (95.81%)	186 (96.37%)
2	No. of residues in outlier region	0 (0%)	1(0.52%)	3 (1.40%)	0 (0%)
3	Ramachandran Z- score	−0.01 ± 0.58	−1.29 ± 0.59	−0.061 ± 0.51	−0.01 ± 0.58

skin permeable level, bioavailability, and Lipinski violations of selected inhibitors were tabulated in Table 4a and b.

3.4. Docking Studies

Discovery Studio Visualizer recognized the active site regions in the modelled proteins. Docking studies of selected chemical and natural compounds were completed using PyRx docking software. The selected vitamins as the chemical compounds for coat protein interaction are well-known activators in different plants' defense mechanisms [15], as well as flavonoids functions against bacterial infection [16]. Flavonoids represent the active player as signaling molecules in the plant microorganism interactions [17]. The characteristic functions of flavonoids are detoxification agents, scavenge ROS, H_2O_2, and toxic metals and, radiation stress suppressors [18,19]. These flavonoids are borne defense mechanisms and function as phytoalexins to respond against microbial infections [20]. The findings were analyzed, the binding energy and the hydrogen bonding regions were established after the docking studies were performed, as shown in Table 5a and b.

3.5. Calculations of Ligand Interaction

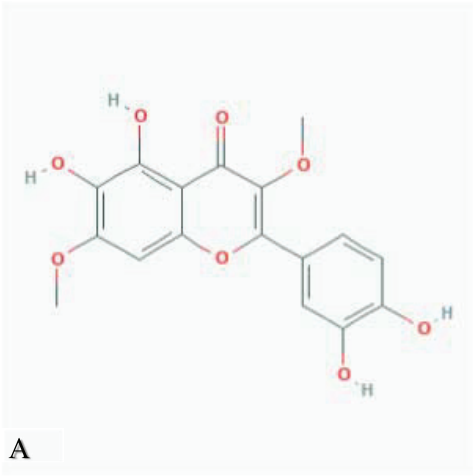
Discovery Studio Visualizer calculated interactions between proteins with ligands. The interaction of chemicals and flavonoids with each protein offers a means to examine each atom of ligands and proteins involved in this interaction. As compare with selected chemical compounds, flavonoids showing good affinity with proteins. A portrayed view of 2D interaction was shown in Figure 6. India_coat protein affinity with ampicillin has two hydrogen bonds and one weak pi-pi interaction, although Agathisflavone forms one ionic bond and pi-pi interaction bond. An interaction with Oman_coat protein Agathisflavone and albendazole in flavonoids were shown promising results. Agathisflavone formed an interaction with three amino acids by two hydrogen bonds and ionic bonds, whereas albendazole has four hydrogen bonds and

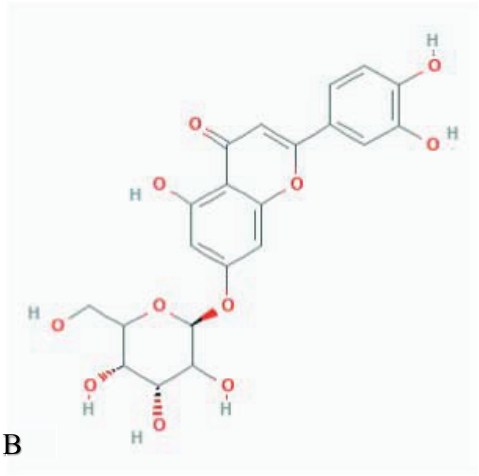
Table 4: a) ADME properties of flavonoid compounds.

Molecule	MW	ESOL Log *S*	ESOL class	GI absorption	BBB permeant	log *Kp* (cm/s)	Lipinski #violations	Bioavailability Score
Agathisflavone	538.46	−6.75	Poorly soluble	Low	No	−6.01	2	0.17
Luteolin 7-O-beta-Dglucosiduronic Acid	462.36	−3.41	Soluble	Low	No	−8.43	2	0.11
3,4,5,6-tetrahydroxy-3,7-Dimethoxyflavone	346.29	−3.81	Soluble	High	No	−6.67	0	0.55
Quercetin 7-O-beta-Dglucoside	464.38	−3.04	Soluble	Low	No	−8.88	2	0.17
Swertianolin	436.37	−3.01	Soluble	Low	No	−8.52	2	0.17
Catiguanin B	482.44	−4.34	Moderately soluble	Low	No	−7.67	1	0.55
Prunin 600-O-gallate	586.5	−4.13	Moderately soluble	Low	No	−8.98	3	0.17
3,4,5-trihydroxy-3-methoxyflavon-7-olate	315.25	−3.88	Soluble	High	No	−6.3	0	0.56

Table 4: b) ADME properties of chemical compounds.

Molecule	MW	ESOL Log *S*	ESOL Class	GI absorption	BBB permeant	log Kp (cm/s)	Lipinski #violations	Bioavailability Score
Albendazole	376.36	−1.31	Very soluble	Low	No	−9.63	0	0.55
Ampicillin	349.4	−1.15	Very soluble	Low	No	−9.23	0	0.55
Atropin	289.37	−2.67	Soluble	High	Yes	−6.77	0	0.55
Iso	614.64	2.61	Highly soluble	Low	No	−16.43	3	0.17
Neomycin	211.26	1.02	Highly soluble	High	No	−10.07	0	0.55
Riboflavin	265.33	−3.23	Soluble	High	No	−5.92	0	0.55


A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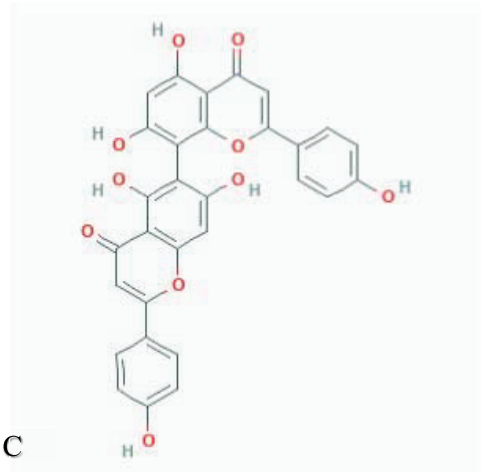
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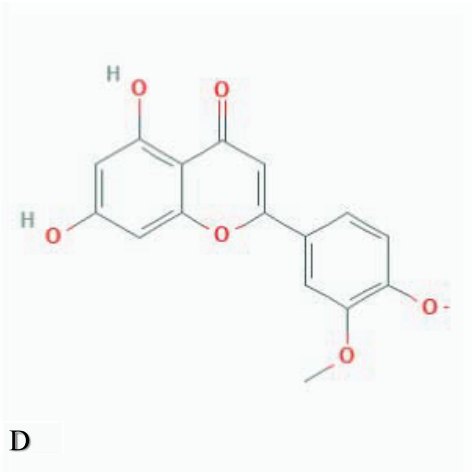
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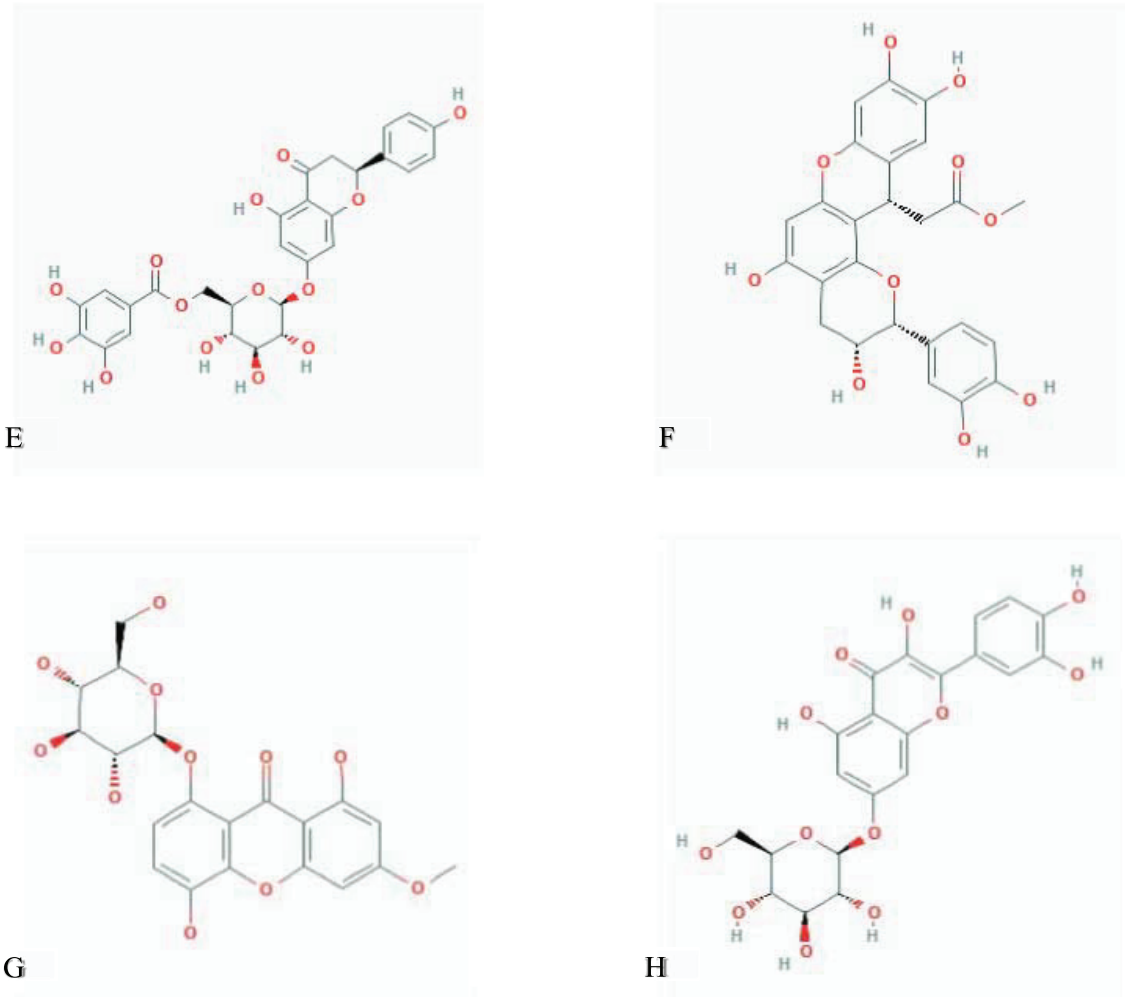


Figure 4: 2D structure of ligands. A) 30,40,5-trihydroxy-3-methoxyflavon-7-olate, B) Prunin 600-O-gallate, C) Catiguanin B, D) Swertianolin, E) Quercetin 7-O-beta-dglucoside, F) 30,40,5,6-tetrahydroxy-3,7-dimethoxyflavone, G) Luteolin 7-O-beta-dglucosiduronic acid, and H) Agathisflavone.

an ionic bond. A CP obtained from the Pakistan sequence has five hydrogens. One ionic bonding with ampicillin and prunin 600-O-gallate has interacted with CP by forming four hydrogen bonds that include 1 weak hydrogen bond, one pi-pi interaction bond, and finally, one unfavorable donor-donor interaction with TYR219. Agathisflavone makes 3 weak pi–pi interaction bonds, three hydrogen bonds, and one ionic bond with Sri Lanka CP. Even albendazole has four hydrogen bonds, one ionic, one Pi-sulfur bond, and unfavorable donor-donor (CYS91) with Sri Lanka CP. The interaction between proteins and ligands with distance values were shown in 2D Figures.

RNA interference (RNAi), systemic antiviral defense, DNA methylation, neurotic resistance, systemic acquired resistance response development, secondary metabolites in plants are the plants' viral immune response against pathogens [21]. Flavonoids showed a significant defense against coat proteins in comparison. The plant develops flavonoids while it indulges in stress conditions [22]. Flavonoids serve as a conventional eastern medicine with anti-inflammatory, antioxidant, anti-tumor, and antiproliferative activities [23].

Our research examined plant flavonoids and chemical inhibitors using the computational-based docking system with pathogenicity determinant CP, AV1. As a need of three-dimensional structure of the protein for docking analysis. There was no determination of the structure of the AV1 protein, so we developed this protein model by homology modelling method.

Different online servers then analyzed the consistency and stereochemistry of the computer-generated model of AV1. For docking analysis, the protein structure in the .pdb format is used. The binding energy and the optimal posture of the molecule for protein binding are expected in the docking study. Our emphasis in the current study was to discover the role of natural flavonoids and chemical inhibitors against the AV1 CP. For this reason, eight flavonoids, i.e., Swertianolin, 3′,4′,5-trihydroxy-3-methoxyflavon-7-olate, Agathisflavone, Catiguanin B, 3′,4′,5,6-tetrahydroxy-3,7-dimethoxyflavone, quercetin- 7-O-[alpha-L-rhamnopyranosyl(1->6)-beta-D-galactopyranoside], prunin 600-O-gallate and luteolin 7-O-beta-D-glucosiduronic acid, were obtained as a potential inhibitor of AV1 based on best docking scores against the active site of AV1. These flavonoids have long been known to suppress

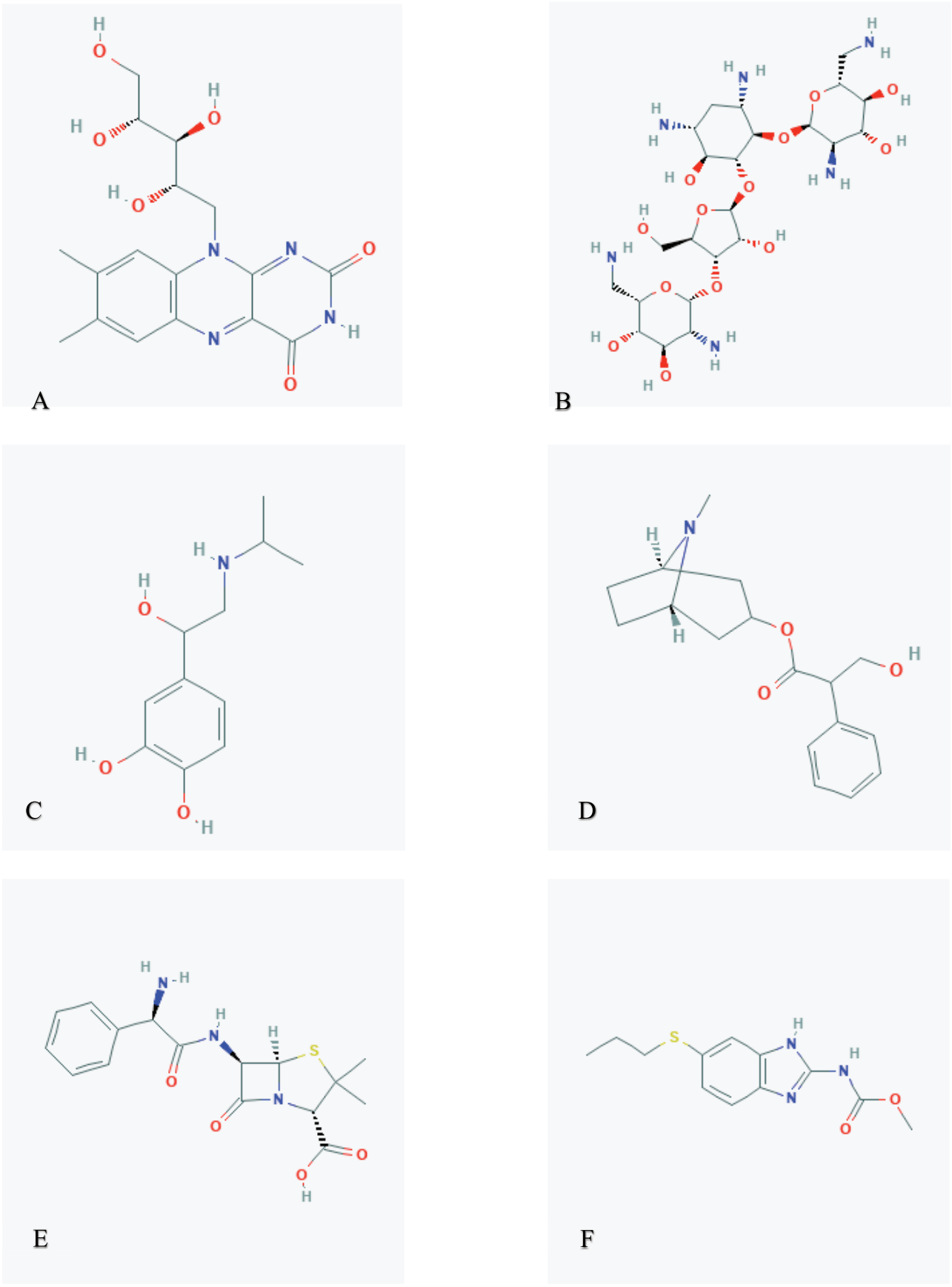


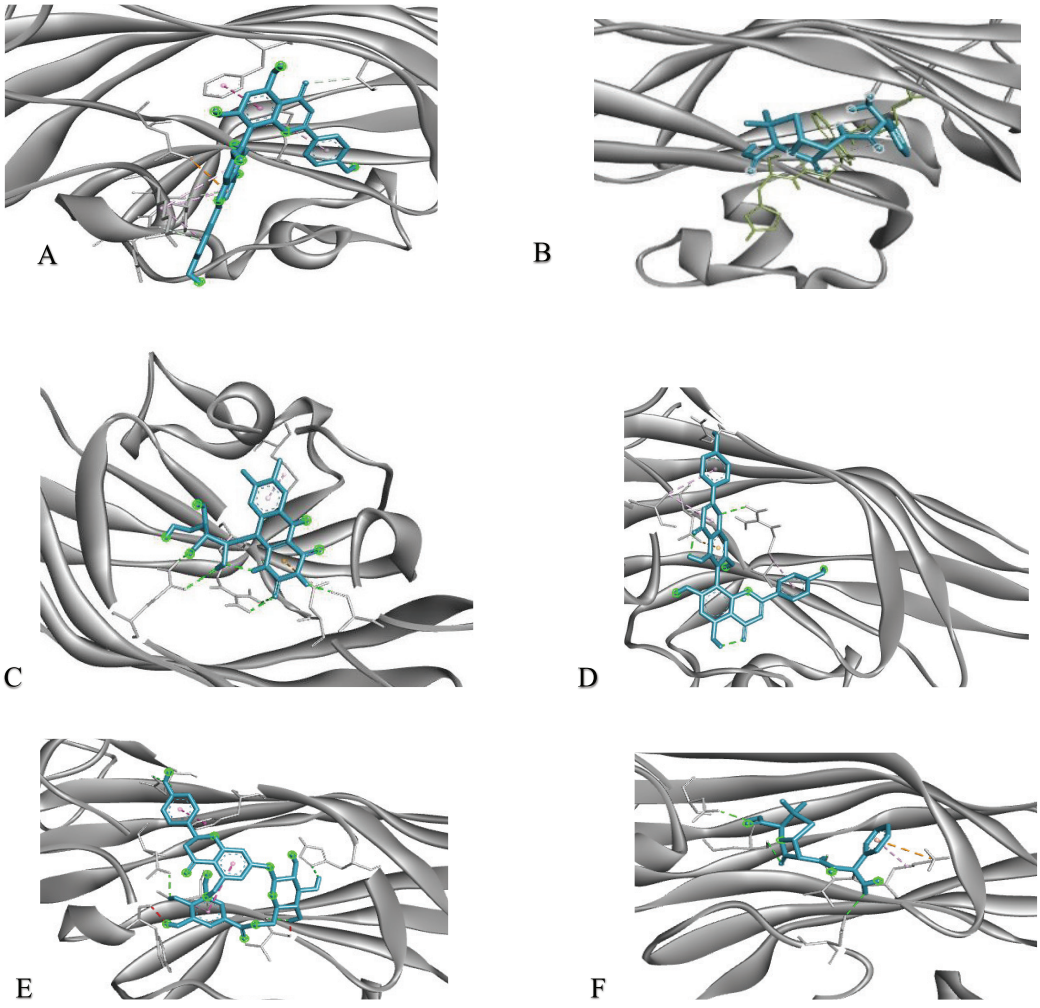
Figure 5: 2D Structure of ligands. A) Riboflavin, B) Neomycin, C) Isoproterenol, D) Atropine, E) Ampicillin, And F) Albendazole.

Table 5: a) Binding energy(kcal/mol) of ligands with proteins (flavonoids).

Compound Chem ID	India (kcal/mol)	Oman (kcal/mol)	Pakistan (kcal/mol)	Sri Lanka (kcal/mol)
Agathisflavone_2512	−8.2	−7.6	−7.3	−7.0
Luteolin 7-O-beta-dglucosiduronic Acid_18128	−4.2	−4.6	−4.5	−4.5
3,4,5,6-tetrahydroxy-3,7-dimethoxyflavone_27767	−6.1	−6.2	−6.0	−6.3
Quercetin 7-O- β –D-glucoside_28529	−3.9	−4.3	−4.1	−4.2
Swertianolin_ 65478	−3.9	−4.3	−4.1	−4.2
Catiguanin B_65602	−7.3	−6.3	−6.9	−6.5
Prunin 600-O-gallate 73787	−7.6	−7.5	−7.5	−6.8
30,40,5-trihydroxy-3-methoxyflavon-7-olate 57928	−5.8	−6.0	−6.0	−5.9

Table 5: b) Binding energy(kcal/mol) of ligands with proteins. (Chemical compounds).

Compound	India (kcal/mol)	Oman (kcal/mol)	Pakistan (kcal/mol)	Sri Lanka (kcal/mol)
Albendazole	−3.9	−5.3	−6.0	−6.1
Ampicillin	−4.6	−5.2	−6.1	−5.9
Atropine	−4.0	−4.6	−5.6	−5.4
Isoproterenol	−0.2	1.3	−5.5	−5.5
Neomycin	−3.9	−5.0	−4.8	−4.9
Riboflavin	−3.9	−4.7	−5.0	−5.0



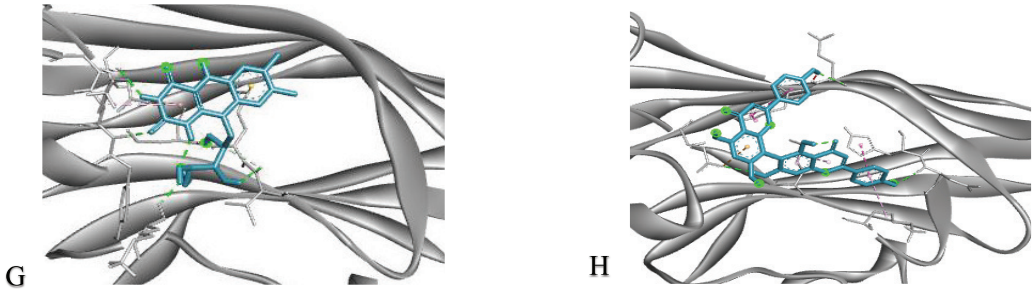
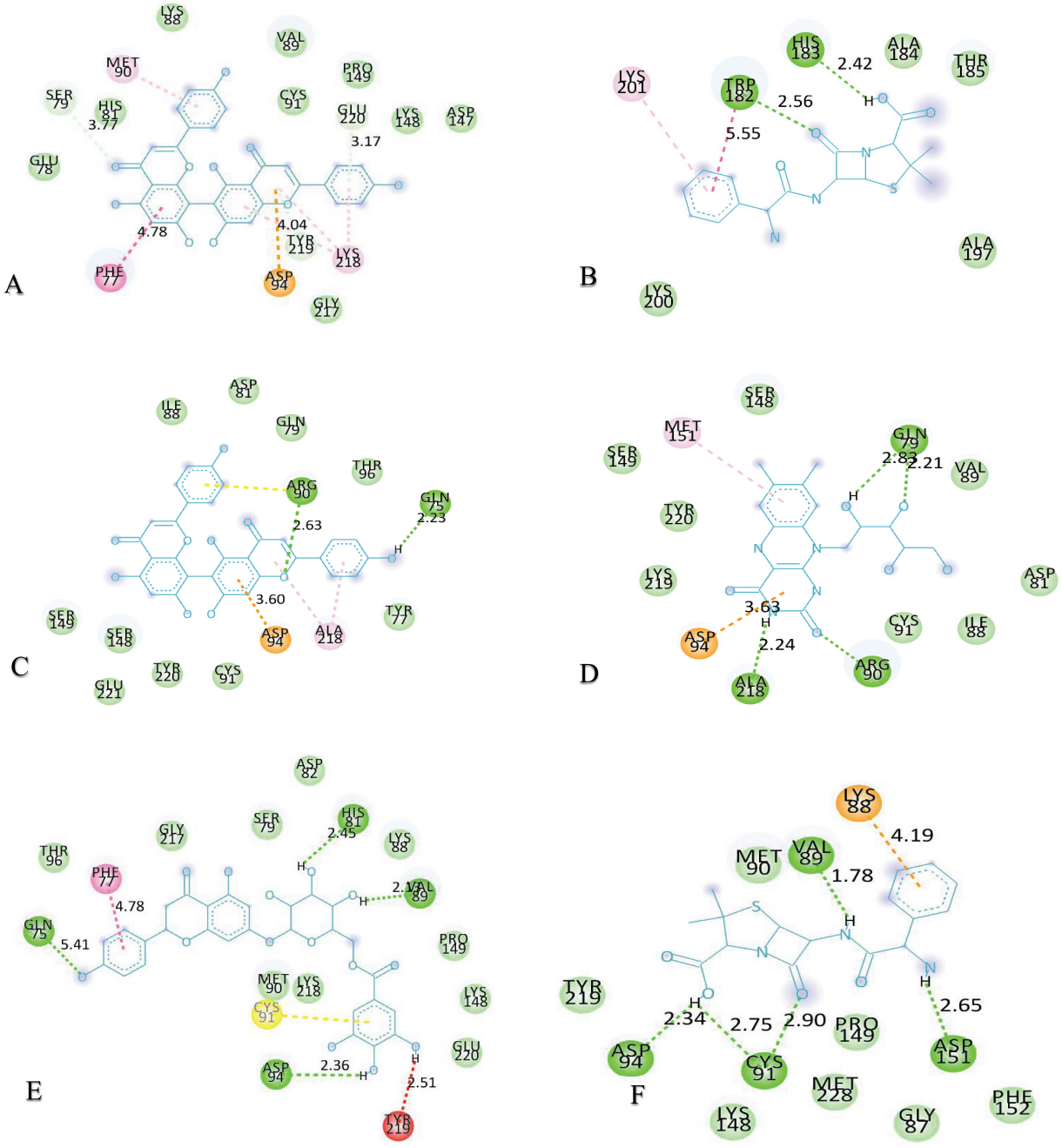


Figure 6: 3D structure of proteins interacting with Ligands. A) and B) India_coat protein with Agathisflavone and Ampicillin. C) and D) Oman_coat protein with ligand Agathisflavone and Albendazole. E) and F) Pakistan_coat protein with ligand Prunin 600-O-gallate and ampicillin. G) and H) Srilanka_coat protein with ligand Agathisflavone and Ampicillin.



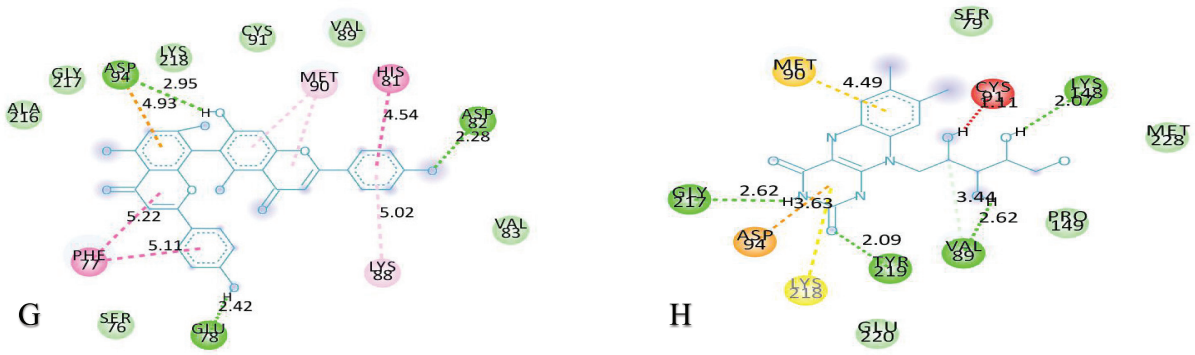


Figure 7: 2D structure of proteins interacting with ligands. A) and B) India_coat protein with Agathisflavone and Ampicillin. C) and D) Oman_coat protein with ligand Agathisflavone and Albendazole. E) and F) Pakistan_coat protein with ligand Prunin 600-O-gallate and ampicillin. G) and H) Srilanka_coat protein with ligand Agathisflavone and Ampicillin.

alpha-amylase and lipase activity [24], inhibit dioxygen or peroxide antioxidant activity reactions [25], the inhibitory activity of acetylcholinesterase and monoamine oxidase [26], enzymatic activity [27], hepatoprotective activity [28], antioxidative activity [28,29]. Flavonoids 3′,4′,5,6-tetrahydroxy-3,7-dimethoxyflavone, and prunin 600- O-gallate has some unknown role. Flavonoid luteolin 7-O-beta-D-glucosiduronic acid has antimalarial activity [30] and radical scavengers' activity [31]. The ChiLCV infection is intensified by the AV1 protein and involves spreading the virus from cell to cell. It interacts with different host cell machinery proteins to increase viral replication in host cells, resulting in symptom intensity.

Our research indicates the possible role of flavonoids as AV1 inhibitors. The flavonoids will be hyper-produced to grow virus-resistant crops as further work is performed on the flavonoid inhibition studies. This research offered a new horizon for the scientists working on the plant defense mechanism against viruses and engineering resistance against these viruses.

4. CONCLUSION

For economically valuable crops such as chilli, ChiLCV causes considerable harm. It leads to a tremendous loss in crop production. Approximately, there are more than 400 species of pathogenic plant viruses that lead to considerable losses in yield and quality. In this research, four different CP of the same continent countries were analyzed and concluded as more conserved regions and sequence similarity. After screening different flavonoids and chemical compounds against viral CP AV1, we conclude that flavonoids act as a potent inhibitor against ChiLCV CP with more binding affinity than chemical compounds. These ligand molecules were prescreened for ADME properties to test their drug-likeness and bioavailability and showed no harmful effects while consuming economically prized crops end-products by a human. As the plant itself secretes these flavonoids, there is no harm to host plants. This study might be interesting for enhancing the inbuilt resistance in plants against ChiLCV. It has illustrated the interactions of ChiLCV CP with plant secreted compounds, such as flavonoids and their role in plant defense mechanism.

5. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

6. FUNDING

There is no funding to report.

7. CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

8. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

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How to cite this article:
Jeyaraj G, Mohideen HS, Geetanjali AS. *Ab-initio* modeling and docking evaluation of geographically derived coat proteins of chilli leaf curl virus with flavonoids and chemical compounds. J Appl Biol Biotech 2021;9(S1):40-51.