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Research Article

MOLECULAR DOCKING STUDIES OF PLANTS DERIVATIVES ISOLATED FROM PLANT SOURCES TARGET FOR CHIKUNGUNYA VIRUS

P. Praveena[1], P. Agastian[1], D. Sudarsanam[2], S. Ignacimuthu [3], Jennifer Ambrose[3]

[1]Department of Plant Biology and Biotechnology, Loyola College, Chennai
[2]Department of Advanced Zoology and Biotechnology, Loyola College, Chennai
[3]Entomology Research Institute, Loyola College, Chennai
Corresponding author Email.com: praveena.bioinformatics2009@gmail.com

ABSTRACTS

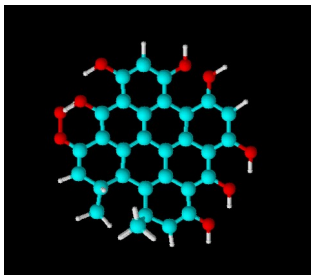
Chikungunya virus causes fever in humans and produces severe joint pain. So far no drug has been specifically developed to treat chikungunya virus. Some medicinal practioners prescribe a herbal drug prepared from *Eupatorium prostratum*. Eupatorin 200 is the main phytochemical in this plant. Using this ligands we carried out docking with target structural polyprotein. The results showed that eupatorin docked strongly with the target indicating that the use of this plant to treat chikungunya has some scientific basis.

KEY WORDS: Drug target, Chikungunya virus; *Euphorbia prostrata* (Eupatorium 200).

INTRODUCTION

Chikungunya fever is a viral disease transmitted to humans by the bite of infected *Aedes aegypti* mosquitoes; they also transmit dengue and yellow fever [1,2]. Chikungunya virus is a member of the genus Alpha virus belonging to the family Togaviridae. Historical accounts of the epidemics of fever, artharalgia, swelling of joints resembling chikungunya fever have been recorded as early as 1824 in India and elsewhere. Chikungunya fever was first described in 1952-1953 in febrile patient in Tanzania following the outbreak in Makonde plateu, along the border between Tanzania and Mozambique [4, 5]. Since then chikungunya epidemics have been reported from several countries in Africa, Asia and elsewhere. In India it has been documented in several states [6, 7). Chikungunya fever affects all age groups and sexes. The incubation period ranges from 3-12 days (usually 3-7

days). The onset is usually abrupt and sudden with high fever, severe artharalgia, and myalgia and skin rash [5]. Treatment of chikungunya fever is symptomatic and supportive which include paraceptomol dicyclofenic or hydroxyl chloroquine [8]. Some herbal physicians have recommended the use of *Eupatorium prostratum*. Eupatorin is the main compound isolated from this plant.Euphorbia prostrata is a species of euphorbia known by the common name prostrate sandmat. It is native to the West Indies and certain parts of South America, but it is widely naturalized in many other parts of the world, where it can be found in varied habitat types and in many areas grows as a roadside weed. This is an annual herb producing slender prostrate stems up to about 20 centimeters long, sometimes purple-tinted in color.[1] The oval-shaped leaves are up to a centimeter long with finely toothed edges. The inflorescence is a cyathium less than 2 millimeters wide, with white petal-like appendages surrounding the actual flowers. There are four male flowers and a single female flower, the latter developing into a lobed, hairy fruit one to two millimeters wide.This study was aimed at finding the suitability of eupatorin to treat chikungunya virus using Bioinformatics tools.



Chemical structure viewed in a Mol format view. Fig 1 a.

MATERIALS AND METHODS

It has been found that all the Chickungunya virus types have 5 structural proteins located in the envelope, nucleocapsid. The viral envelope contains 3 integral membrane proteins. From the pathogenicity of the virus structural polyprotein has been found to have a major role. Hence we selected structural polyprotein as the target. Once the target protein was identified its molecular crystallographic 3D structure was collected from the SWISS 3D modeling databank. The target protein, structural polyprotein, did not have an original crystallographic structure; therefore, an automated molecular model was generated.The homology model of *Chikungunya* virus structural polyprotein was built using SWISS PDB viewer. The protein sequence (320 residues long 360 amino acids) from chikungunya virus structural polyprotein was retrieved from GenBank FASTA format. Using the basic local

alignment search tool BLAST at PDB for chikungunya Structural polyprotein we identified a template structure (Fig. 3 A and B). We then incorporated the structural polyprotein from the template structure into the modeled structure .The atomic charges of the amino acid side chains involved in structural polyprotein coordination system is similar to those of the template (Fig. 4). Structural refinement through energy minimization model was performed using **Swissprot Protein database viewer.** The constructed model of structural polyprotein from chikungunya virus was examined for validation using different criteria. The RMSD analysis of the developed model was evaluated by means of deviation from its template using SUPERPOSE. The stereo chemical quality of the predicted model was evaluated using Structural Analysis Verification Server (SAVS). Protein quality was predicted using PRO-Q. Ramachandran plot was also determined. Docking were performed using Docking Server. ProtParam computes various physico-chemical properties that can be deduced from a protein sequence. No additional information is required about the protein under consideration. The protein can either be specified as a Swiss-Prot/TrEMBL accession number or ID, or in form of a raw sequence. White space and numbers are ignored. If you provide the accession number of a Swiss-Prot/TrEMBL entry, you will be prompted with an intermediary page that allows you to select the portion of the sequence on which you would like to perform the analysis. The choice includes a selection of mature chains or peptides and domains from the Swiss-Prot feature table (which can be chosen by clicking on the positions), as well as the possibility to enter start and end position in two boxes. By default (i.e. if you leave the two boxes empty) the complete sequence will be analyzed. Second copy of the sequence to the first), as all computations performed by ProtParam are based on either compositional data, or on the N-terminal amino acid. Once the target was selected, we identified chloroquine phosphate and Eupatorin (Figs. 1 and 2) as ligands to study their potential to control chikungunya virus.

Eupatorium prostratum

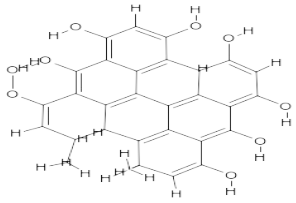


Fig 2.

Docking Server offers a web-based, easy to use interface that handles all aspects of molecular docking from ligand and protein set-up. While its user friendly interface enables docking calculation and results evaluation carried out by researchers coming from all fields of biochemistry, Docking Server also provides full control on the setting of specific parameters of ligand and protein set up and docking calculations for more advanced users.The application can be used for docking and analysis of single ligands as well as for high throughput docking of ligand libraries to target proteins.

Docking Server integrates a number of computational chemistry software specifically aimed at correctly calculating parameters needed at different steps of the docking procedure, i.e. accurate ligand geometry optimization, energy minimization, charge calculation, docking calculation and protein-ligand complex representation. Thus, the use of Docking Server allows the user to carry out highly efficient and robust docking calculations by integrating a number of popular software used in in silico chemistry into one comprehensive web service.

Results

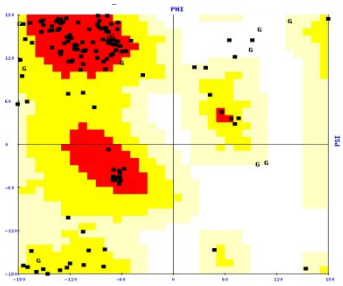
Chikungunya structural polyprotein had the following compositions

Molecular weight =-137270.7 Daltons protein sequence length 360 amino acids Ala(A) 102=8.2%, Arg 59 (4.8%), Asn 54 (4.4%), Asp 44 (3.5%), Cys 49 (3.9%), Gln 52 (4.2%), Glu 61 (4.9 %), Gly 6.2%, His 42 (3.4%), Ile 61 (4.9%), Leu 82 (6.6%), Lys 74, (6.0%), Met 30 (2.4%), Leu 82 (6.6%), Lys 74, (6.0%), Met 30 (2.4%), Phe 34 (2.7%), Pro 91 (7.3%), Ser 72 (5.8%), Thr 92 (7.4%), Trp 15(1.2%), Tyr 49(3.9%), Val 101(8.1%).

The Cα RMSD and the backbone RMSD deviations for the model and the template crystal structure were 0.36 A° and 0.42 A° respectively.

The protein quality evaluated using structural Analysis verification server exhibited the following characteristics: Predicted LGscore : **-1.110** Predicted MaxSub : **-0.501 (**LGscore>1.5 fairly good model LGscore>2.5 very good model LGscore>4 extremly good model MaxSub>0.1 fairly good model MaxSub>0.5 very good model MaxSub>0.8 extremly good model). Ramachandran plot yielded good match results (Fig. 3).

Residue Range 407: ALA -> 549: ASN



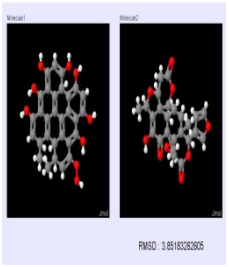


Fig 4 a. Fig 4 b.

Plot statistics

Residues in most favoured regions [A,B,L]	314	85.1%
Residues in additional allowed regions [a,b,l,p]	54	14.6%
Residues in generously allowed regions [~a,~b,~l,~p]	1	0.3%
Residues in disallowed regions	0	0.0%
Number of non-glycine and non-proline residues	369	100.0%
Number of end-residues (excl. Gly and Pro)	9	
Number of glycine residues (shown as triangles)	51	
Number of proline residues	21	
Total number of residues	450	

Based on an analysis of 118 structures of resolution of at least 2.0 Angstroms and R-factor no greater than 20%, a good quality model would be expected to have over 90% in the most favoured regions.

Fig 4 c. Ramachandran Plot.

Figure 3 depict the structural polypolyprotein identified using SWISS PDB; it also shows the predicted model of the template

Accessible surface area (ASA) analysis of the predicted

structural polyprotein showed the active site amino acid as follows (Fig. 5). Some of the ligand binding residues and metal ion binding residues were found to have high Ala: 1.420 Arg: 0.980 Asn: 0.670 Asp: 1.010 Cys: 0.700 Gln: 1.110 Glu: 1.510 Gly: 0.570 His: 1.000 Ile: 1.080 Leu: 1.210 Lys: 1.160 Met: 1.450 Phe: 1.130 Pro: 0.570 Ser: 0.770 Thr: 0.830 Trp: 1.080 Tyr: 0.690 Val: 1.060 : 0.840 : 1.310 : 1.000.

Eupatorin docked with receptor complexes and were identified via docking by using Docking Server. The drugs were docked with the receptor using the above parametersDocking results were tabulated between structural polyprotein receptor andtheconventional drug Eupatorin. Eupatorin on docking withstructural polyprotein

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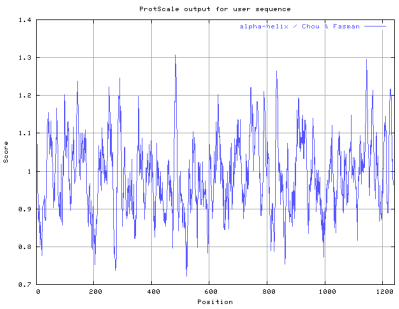
produced energy values **6.13 kcal/mol** of respectively (Fig. 9). This way the pharmacophoric part of the drug was partially identified.



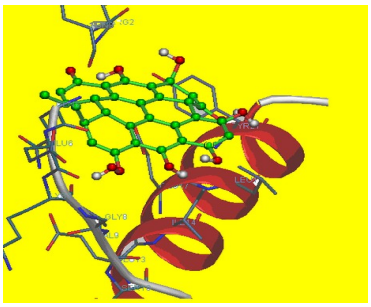


Fig 9. Docking

Docking results were tabulated between structural polyprotein receptor and the conventional drug and Eupatorin. Eupatorin on docking with structural polyprotein produced energy values of -113.15 and -107.19 respectively (Fig. 6 A and B). It was observed using RasMol that the carbonyl groups present in the drug was the site of binding to the receptor (2IOK) and methyl group present in the probable functional groups resulted in a decrease in the energy values. This way the pharmacophoric part of the drug was partially identified.

DISCUSSION

Bioinformatics tools are having the potential to significantly improve how drugs are found, brought to the clinical trials and eventually released to the marketplace.

Bioinformatics approaches were applied to identify the potential drug target in Chickungunya virus**.** Chickungunya virus has emerged as a major epidemic disease in the tropical and subtropical countries. In the present study, data mining was used to identify potential targets from the literature as well as using *in silico* prediction.

In the present study, the BLAST results clearly showed the sequence similarity of chikungunya vius with other organisms. Almost all the organisms that possessed similar protein coding sequences are pathogens.Docking allows the scientist to virtually screen a database of compounds and predict the strongest binders based on various scoring functions. The molecules binding to a receptor, inhibit its function, and thus act as drug. This study indicated that Eupatorin isolated from *Eupatorium prostratum* has higher affinity to the protein binding site. Clinical trials should be conducted to confirm the efficacy of the compound to control Chikungunya Virus.

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