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Full Length Research Article

Molecular Docking Studies on Plant Derived Bioactive Compounds

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Abstract

In the current scenario medicinal products from natural source have been significantly contributing towards the therapeutic approach in the treatment of diseases ranging from simple to complicate. The utilization of herbal products has slowed down due to lack of standardization involving botanical, chemical and biological (activity /toxicity) aspects. Hence a computational technique incorporating in silico molecular docking simulation study has become an essential tool for drug discovery, standardization and screening of phytochemicals. In this molecular docking study, the ligand – protein interaction of pure active phytol against the targeted fusarium protein is done.

***Key words*:** Phytol, Antifungal, Protein, Modelling, Ligand structure, Phytocompounds

Plant diseases are causes major threats to the economically important crops globally. Among these, major diseases are caused by fungal pathogens. The fungal pathogens play a crucial role in both quantity and quality and profitability of plant production. Fungal pathogens affect all kinds of vegetable crops and it mainly affects cassava which is highly rich in carbohydrate content. Cassava is a major source of dietary energy for more than 500 million people [1]. Cassava is a nutrient dense, starchy root vegetable consumed in developing countries around the world. It is known as the highest producer of carbohydrate among the stable crops. Even during droughts, the plants tolerate low soil fertility and low intensity management. Cassava production is hampered by many factors among which diseases such as root rot are important [2]. Root rot occur on young or old cassava plants and can be caused by members of one or several fungal genera. Disease is incidence usually in higher during the rainy season (3). The main symptom of rot disease is break down in tissues of the mature tuberous roots, usually associated with foul order and change in colour, which may be useful in distinguishing the pathogens involved. Storage tissue of tuberous roots primarily infected by a *fusarium sp*, *Rhizopus sp*, *A. niger*, *A. flavus*, *Mucor sp*, *Phytophthora sp.* etc., from these reports, it is not possible to determine which genus is most important economically, but there is general agreement that *Fusarium sp* are the important components of the fungal complex that causes cassava root rot everywhere where cassava is cultivated.

These fungal pathogens are controlled by fungicides which are harmful to the humans and animals when entering the food chain. The fungicides are often explored with hesitation as they exhibit side effects. This strategy is overcome by selecting suitable herbal products [4]. In India, herbs are used as traditional medicines which contains various bioactive compounds that exhibits antibacterial, antifungal, anticancer, anti-inflammatory and antioxidant properties [5].

Plant based medicines are often prepared from crude plant extracts comprising of a complex mixture of different phytochemicals [6]. My research is with the help of *Andrographis paniculata* which is highly rich in phyto compounds we can control the fungal pathogens. *Andrographis paniculata* (Burm.f.) Wall ex Nees (Acanthacea) is an annual herbaceous plant native to India and Srilanka. It is widely cultivated in southern eastern Asia, where it has been traditionally used to antifungal, antibacterial and some infectious diseases [7-8]. Mostly the leaves are used for medicinal purposes. *Andrographis paniculate* is an erect annual herb extremely bitter in taste in all parts of the plant body. The genus *Andrographis* consists of 28 among them only a few species are medicinal, of which *Andrographis paniculate* is the most popular.

The preliminary phytochemical screening of *Andrographis paniculata* revealed the presence of phytoconstituents like alkaloids flavonoids, phenols and tannis. In Gcms analysis, Benezone, 1, 2,3, - trimethoxy-5-(2 – propenyl)-, Cyclopenta (c)Pyran – 4 - Carboxylic acid, 7 – methyl ester and 9,12,15 – Octadecatrienoicacid, Phytol and methyl ester, (Z,Z,Z)- covered the high areas, that might be responsible or can possess the antifungal activity against. Currently, the in-silico analysis is an effective and inexpensive method for designing and testing drugs. This technique provides information about drug receptor interactions that are useful to predict the binding orientation of drug candidates to

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their target proteins [9]. This approach helps in systematic study by introducing a molecule on the binding spot of the object macromolecular-receptor covalent fashion, leading to an accurate binding at the active sites of each ligand. Additionally, molecular docking is often used to find potential compounds that can act as inhibitors of disease agents, such as fungal pathogens [10]. The aim of this study is to investigate inhibitory concentration of fungal pathogens like *fusarium*. In general plants are derived from non-phytotoxic and potentially effective against all fungal pathogens. Phytol, chlorophyll derived diterpene essential oil found abundantly in nature. Phytol is used as various important biological activities including anti diabetic, anti-inflammatory, anti-arthritic anticonvulsant, anti plasmodic, anti-microbial and anti-mutagenic. The objective of this study is to determine the activity of phytol and its derivatives against fungal cell wall protein. Some of the computational tools are used for this purpose to investigate the best ligand and optimized receptor protein as the best choice for the future researchers.

MATERIALS AND METHODS

Drug docking

The present investigation is to perform the molecular drug protein interaction studies on fumonisin biosynthesis cluster protein 1 (fusarium) with Phytol chemical compound using insilico drug docking tools.

Methods

i) Protein modelling
ii) Drug 3D prediction.

Protein modeling

The protein sequence of *Fumonisin biosynthesis cluster protein 1 (Fusarium Sp*.) is entered into PFAM, a domain analysis server (https://pfam.xfam.org/). Then, the sequence is applied into an automated homology modelling server, Swiss Model (https://swissmodel.expasy.org/) for the conversion of the amino acids sequence into 3D structure. The modell protein 3D structure is validated using ProCheck server (https://saves.mbi.ucla.edu/) and viewed using the molecular visualization software, and Discovery studio software.

Drug 3D prediction

In this project, we chose a potential existing molecule, Fluconazole, (CID: 3365) which was retrieved from NCBI – PubChem (https://pubchem.ncbi.nlm.nih.gov/) and the results are obtained for the GC –MS instrument test compound, Phytol (CID: 5280435) to carry out molecular drug docking studies. The 2D drug is converted into 3D structure using Cheminformatics protocols.

RESULTS AND DISCUSSION

The selected protein target (FUM1_GIBM7:W7LKX1) was retrieved from UniProt database in FASTA format. The length of the protein is 2,586 and its molecular weight is 280,550 Mass(Da) (Fig 1). In the initial step, Protein domain analysis of FUM1 protein (Pfam server [11]) was done in order to identify the functional domains. (Fig 2) clearly elucidated that various multi domain amino acids ranges are present in FUM1. By evaluating the post docking studies, it was identified that the domains play a vital role in protein inhibition and efficiency of drug –protein complex. The 3D structure of the target protein was predicted using an automated homology modelling server, Swiss-Model.

SWISS-MODEL server [12-15] converts the amino acid sequence of *FUM 1* into 3D structure [Fig 3-4]. The predicted structure was visualized using the molecular visualization tool, Discovery studio software. SWISS-MODEL analyses the molecular and structural details of *FUM 1*elaborately for docking. SWISS-MODEL is a server for automated comparative modelling of three-dimensional (3D) protein structures. Waterhouse *et al*. [9] computed models by the SWISS-MODEL server homology modelling pipeline which is based on ProMod3, an in-house comparative modelling engine based on Open Structure. The modelled 3D protein was comprehensively evaluated using ProCheck server [16-17] for the assessment of Ramachandran Plot. After modelling, the 3D structure of the mutated protein was validated using ProCheck server. (Fig 5) shows the assessment of Ramachandran Plot which confirms that there is no error (86.2%) in the modelled protein.

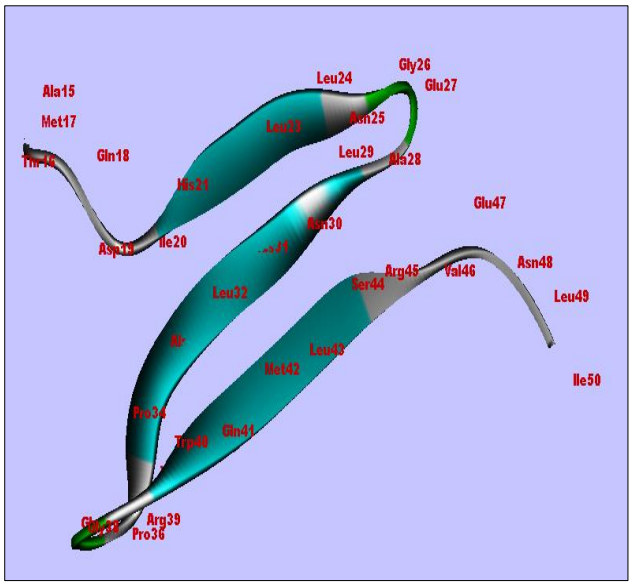

Fig 1 Protein Modelling: 3D structure of FUM 1

The above picture shows the 3D view of the protein structure of *FUM 1* in secondary structure colour with solid ribbon model visualized using Discovery Studio Software.

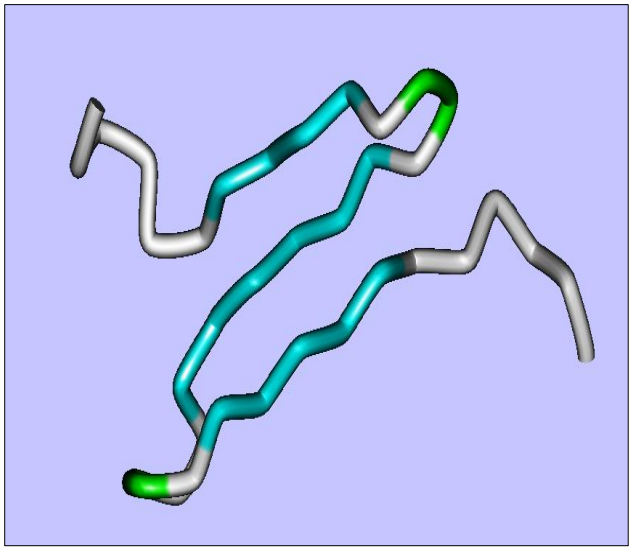

Fig 2 Protein Modelling: 3D structure of FUM 1

The above picture shows the 3D view of the protein structure of FUM 1 shown in secondary structure colour with schematic model visualized using Discovery Studio Software.

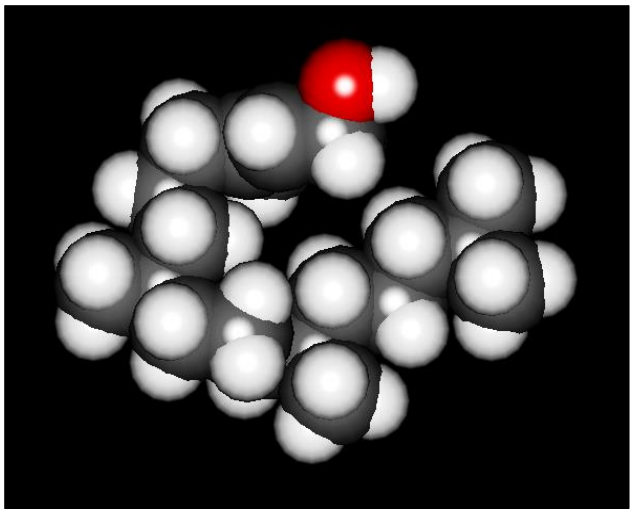

Fig 3 Cheminformatics -3D Structure of Phytol

The above picture shows the 3D structure of Phytol with coloured atoms: Grey-Carbon, Red -Oxygen and White – Hydrogen using Discovery Studio Software.

Receptor	Ligand	Complex Type	Cluste
MATFungal.pdb	Fluconazole.pdb	drug	4.0

Solution No	Score	Area	ACE
1	3192	386.40	-96.78
2	3162	359.30	-42.36
3	3102	355.20	-58.26
4	2940	340.10	-100.03
5	2922	357.70	-110.68
6	2886	356.20	-117.28
7	2880	353.60	-106.49
8	2868	330.80	-149.56
9	2820	321.40	-154.45
10	2752	343.70	-164.93
11	2738	332.90	-92.93
12	2724	329.90	-65.58
13	2676	361.60	-127.61
14	2666	310.00	-116.35
15	2622	289.70	-76.64
16	2614	295.50	-78.20
17	2594	353.10	-130.19
18	2594	296.80	-68.18
19	2590	291.30	-102.51
20	2352	265.90	-48.42

Fig 4 Molecular Drug Docking: FUM 1 with Fluconazole

The above picture represents the Patch Dock result page showing the drug docking score of the control drug, Fluconazole with the modelled protein target, *FUM 1*. The negatively high ACE (Atomic Contact Energy) value is -127.61 kcal/mol.

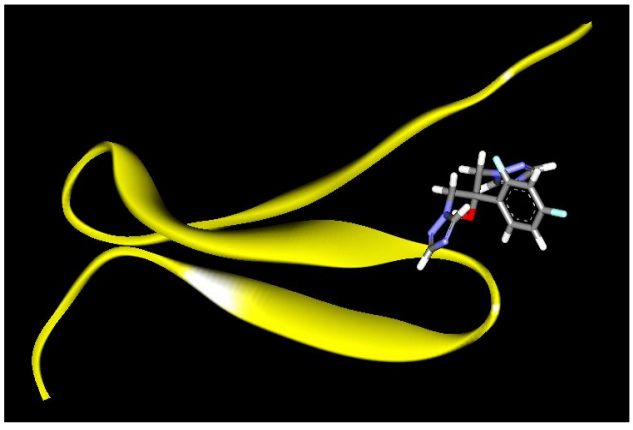

Fig 5 Molecular drug docking

3D structure of FUM 1 with Fluconazole complex

The above picture represents the existing drug molecule (Fluconazole) docked with FUM 1 protein structure. Yellow colour indicates Fluconazolein space-filling model using Discovery Studio Software.

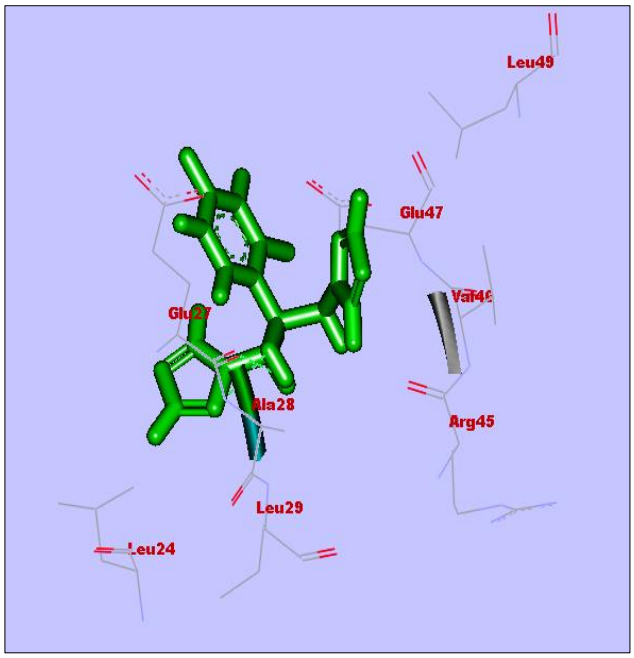

Fig 6 Molecular drug docking

3D structure of FUM 1 with Fluconazole complex

The above picture represents the existing drug molecule docked with FUM 1 protein structure with drug binding amino acids labels. Green colour indicates Fluconazole in Stick model using Discovery Studio Software (H-Bond -Ligand Binding sites prediction: Model).

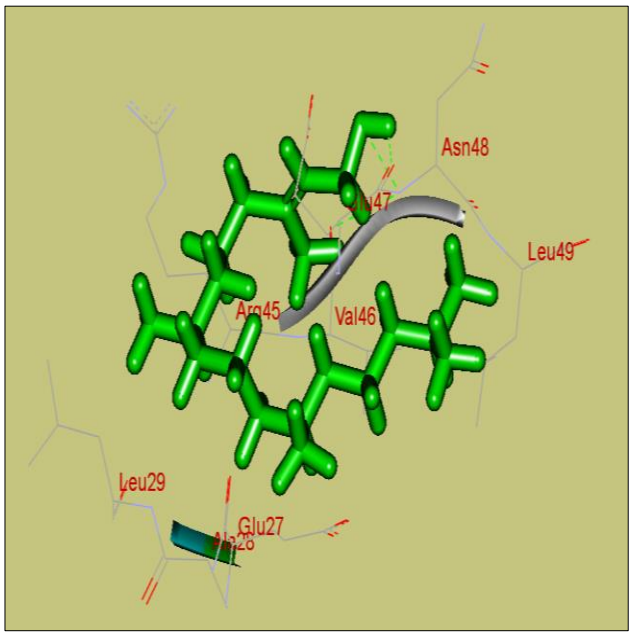

Fig 7 Molecular drug docking

3D structure of FUM 1 with Phytol (H-Bond interaction)

The above picture represents the Test drug molecule Phytol docked with FUM 1 protein structure with drug binding amino acids labels. Green colour indicates Phytol in Stick model using Discovery Studio Software (H-Bond -Ligand Binding sites prediction: Model).

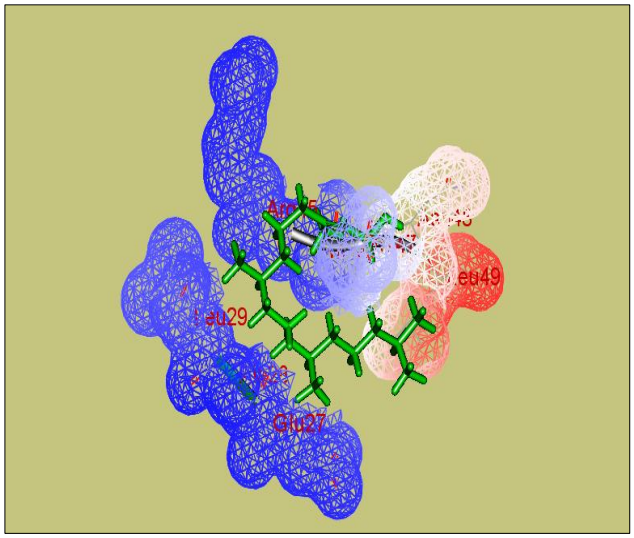

Fig 8 Molecular drug docking

3D structure of FUM 1 with Phytol(H-Bond interaction -1)

The above picture represents the Test drug molecule Phytol docked with FUM 1 protein structure with drug binding amino acids labels. Green colour indicates Phytol in Stick model using Discovery Studio Software. (Vander waals interaction: Model-1).

Table 1 Results of molecular drug docking (Patch dock server)

Target protein	Fluconazole (Control drug)	Phytol
W7LKX1.1 FUM1_GIBM7	-164.93	-202.96
Fumonisin (*Fusarium Sp.*)	Kcal/mol	Kcal/mol

The above table clearly explains that based on the molecular drug docking scores, the selected Phytol molecule is an efficient inhibitor of Fumonisin (*FusariumSp.*) protein when compared to the control drug molecule, Fluconazole.

Mechanism of molecular docking

The 2D structure of Fluconazoleis shown in (Fig 8) and the 3D structure of Fluconazole is shown in (Fig 9). Likewise, the 2D and 3D structure of Phytolare predicted and shown in (Fig 10-11) respectively. The initial step in drug docking procedure is the conversion of 2D to 3D structure. For docking, Discovery Studio Software is made use of to perform automated 2D to 3D conversion. Fundamentally, molecular docking is aimed at predicting the ligand-receptor complex structure using computation methods. Docking (Patch Dock server) [18-21] can be carried out using two inter-connected steps: primarily, by sampling conformations of the ligand in the active site of the protein; secondarily, we rank these conformations via a scoring function. Ideally, sampling algorithms should be able to reproduce the experimental binding mode and the scoring function should also rank it highest among all generated conformations. A brief overview of basic docking theory is given from these points of view.

The present docking algorithm comprises of object recognition and image segmentation techniques used in computer vision. The algorithm comprises of three major stages: 1. Molecular Shape Representation – here, the molecular surface of the molecule is computed. Then, a segmentation algorithm is applied for detecting geometric patches (concave, convex and flat surface pieces). The patches are filtered to retain only patches with 'hot spot' residues. 2. Surface Patch Matching - a hybrid of the Geometric Hashing and Pose-Clustering matching techniques is applied to match the patches detected in the previous step. We match concave patches with convex and flat patches with any type of patches. 3. Filtering and Scoring – we examine the candidate complexes from the previous step. All complexes with unacceptable penetrations of the atoms of the receptor to the atoms of the ligand are discarded. Finally, we rank the remaining candidates as per a geometric shape complementarity score [20-21] (Table 1). The PatchDock results of Phytoldrug with FUM 1 protein shows an atomic contact energy value of -202.96 Kcal/mol (Fig 13-17) whereas, that of the existing drug molecule, Fluconazole with FUM 1 is -164.93 Kcal/mol (Fig 10-12).

Our results clearly elucidate that Phytolis a potential inhibitor of FUM 1 protein. Interestingly, it was clinically proved that the domain regions of FUM 1 is found between 980-1274 (Polyketide synthase dehydratase), 30-279 (Beta-ketoacyl synthase, N-terminal domain), 608-935 (Acyl transferase domain), 2197-2374 (KR domain), 287-403 (Beta-ketoacyl synthase, C-terminal domain), 1465-1569 (Methyltransferase domain), 405-577 (Ketoacyl-synthetase C-terminal extension), 2038-2172 (Zinc-binding dehydrogenase) and 2494-2561 (Phosphopantetheine attachment site) amino acids positions [22]. Our docking results shows that Phytol directly binds within the range of the domain activity region of FUM1 (30 to 279aa) (Fig 18) amino acids positions.

CONCLUSION

This stunning success of pharmaceutical industries in developing new antifungal drug finding consumer friendly antifungal agents for treating broad range of fungal diseases is still a priority, because of flowing multi drug resistant pathogens. One noble approach is to search for effective antimicrobial agents from natural resources particularly the plant resources. In pharmaceuticals plant preparation shows a broad range with antimicrobial effects is one of most important.

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