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In silico Analysis of biomolecules produced by Bacterial Endophyte *Bacillus velezensis* YEBBR6 for the Management of *Fusarium oxysporum* f. sp. *cubense*

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ABSTRACT: Fusarium wilt is a major stumbling block to global banana production, and it is widely regarded as one of the most devastating diseases in agricultural history. Endophytes are organisms reported to be involved in resisting fungal pathogens and promoting growth. These organisms deploy a wide variety of mechanisms to induce resistance in plants. One such mechanism is the production of biomolecules during their confrontation with the pathogen inside the host. These biomolecules can be exploited for their antifungal activity. *Bacillus velezensis* YEBBR6 is one such endophyte isolated from the Panama wilt-resistant cultivar Yengambi KM5 (AAA). Biomolecules produced by them were analyzed for the antagonistic activity against *Fusarium oxysporum* f. sp. cubense using molecular docking approach. Molecular modeling of fungal protein targets and docking studies of those with the selected biomolecules were carried out. Among those screened, cefazolin was found to be having a higher affinity towards all the selected targets. Hence it may be exploited for the management of the disease after the confirmation of the same through wet-lab studies as well as field-level studies.

Keywords: Foc, *Bacillus velezensis* YEBBR6, biomolecules, Molecular modeling, docking, cefazolin.

INTRODUCTION

Banana (*Musaceae*) is one of the most widely cultivated fruit crops in tropical nations, consumed across the world with a wide variety of applications in the food industry. Its massive by-products provide a wonderful supply of extremely valued raw materials for other businesses (Padam, 2012). In India, bananas rank first in terms of fruit production and third in terms of area. Across the world, it's being cultivated in 135 countries and overseas territories in tropics and subtropics, among which India is the largest producer, with the production of about 31504000 tonnes in 2019 (FAOSTAT, 2020). The production and productivity of bananas are imperiled by a destructive disease, Panama wilt brought about by a soil-borne pathogen, *Fusarium oxysporum* f. sp. *cubense* (Stover *et al.,* 1962), which was mentioned as *Foc* by W.C. Snyder & H.N. Hansen (Stover and Simmond 1987). Different races of pathogen emerged at different time periods with the first, *Foc* Race 1, which was identified in Australia in the 1870s at a farm near Brisbane (Bancroft, 1876). During the 1900s it gained importance globally as it spread to America, Africa, and the Far East where the Gros Michael cultivar was grown as a mono-crop. This led to the substitution of the same with the resistant Cavendish cultivar (Pleotz, 2015). But recently, the disease resurfaced in the Southeast Asian continent and Australia in the 1970s with the discovery of a new race of Foc, tropical race 4 (Foc TR4) affecting Cavendish cultivar in subtropics which was earlier resistant to the race 1, when grown under seasonal abiotic stress (Su *et al.*, 1986; Ploetz and Pegg, 1997; Dita *et al.*, 2018). In the tropics it was reported in the 1900s (Ploetz and Pegg 2000; Ploetz, 2006). Since then, the disease has spread throughout Southeast Asia, the Middle East, India, Pakistan, and Africa (Butler, 2013; Zheng *et al*., 2018)

The pathogen is a filamentous- saprophytic hemibiotrophic (Stover, 1962) with more than 20 vegetative compatible groups (Ploetz *et al,* 2011). It colonizes the plant via roots, clogs the vascular tissue, and causes the plant to wilt and eventually die (Pleotz *et al.,* 2015). Reproduction is by vegetative means, and chlamydospores can live for more than 20 years in the

absence of a host by succumbing to extremely hard conditions through thick-walled and desiccation-tolerant chlamydospores, making management more challenging (Dita *et al.,* 2018; Pegg *et al.,* 2019). Very few methods are available to date for the management of the pathogen with available ones not having long-term effects. Chemical methods posethreat to the other organisms in the environment (Gang *et al.,* 2013) and soil sterilization using the same is practically strenuous in large commercial plantations and practiced only in greenhouses or in case of intensive cultivation (Shen *et al.*, 2018). Whereas the existing biological control methods even though it is environment friendly, the lower efficacy against the chlamydospores remains the limitation for their successful application at the field level (Pegg *et al*., 2019). Even though resistant cultivars are an alternative for all the control measures, they could not meet consumer preferences (Mostert *et al.,* 2017).

In various agricultural and horticultural crops, biocontrol strategies including endophytes have been used in integrated disease management (Vinodkumar *et al.,* 2015; Dheepa *et al.,* 2016). Endophytes are microorganisms that live in the tissues of plants for their entire life and have mutualistic interactions with them, as well as those that do not produce any obvious signs of damage to the plant (Santoyo *et al.*, 2016). These endophytes, which are thought to have originated from the rhizosphere, phylloplane microorganisms, or contaminated planting materials (Hallmann *et al.*, 1997), provide their hosts with a variety of benefits, including nutrient intake, plant growth promotion, and disease resistance (Degrassi *et al.*, 2020). They use a variety of strategies to combat pathogens, including mycoparasitism, competition for nutrients or root niches, antibiosis (the creation of secondary metabolites), quorum sensing and signalling, and activating host resistance mechanisms (Ryan *et al.*, 2018). Bacterial endophytes were also reported in bananas. The higher antifungal activity of *Brachybacterium paraconglomeratum* YEBPT2, *Brucella melitensis* YEBPS3, *Bacillus velezensis* YEBBR6, and the one associated with nectar *Bacillusalbus* YEBN2 (61.1 per cent) from resistant cultivar was discovered during a search for those antagonistic to the pathogen in resistant and susceptible banana cultivars (Ravi *et al.,* 2021). Biomolecules produced bythe endophyte *Bacillus velezensis* YEBBR6 was selected for investigating their potential in having antimycotic activity using docking studies that might subsequently be used for the management of the pathogen. This was accomplished by determining the behaviour and interaction of these biomolecules with the chosen fungal protein targets that are essential for either its life or parasitism. Through the *in-silico* method, the mode of action of the same will eventually be revealed.

MATERIALS AND METHODS

Identification of target proteins. Based on literature mining and analysis, targets that were supposed to be required for normal development, pathogenesis, or virulence were chosen. This includes G protein ß subunit (FGB1) (Soundararajan *et al.*, 2011), 5'→ 3´ Exoribonuclease 2 (XRN2) (Maldonado *et al.*, 2018) and Fusarium transcription factor 1 (FTF1) (Ghang *et al.,* 2014) (Table 1). After identifying possible antifungal targets of Foc, the interaction of the ligands with the protein targets was investigated.

Molecular modeling of targets. There were no experimentally validated 3D structures for any of the selected protein targets, so computational modeling was performed using two bioinformatics workspaces. The sequences of targets were initially obtained in FASTA format from the UniProt database and then submitted for BLASTp analysis against the PDB database using NCBI's web BLAST. Query coverage and identity % of the BLASTp analysis resulted sequences were used to select different modeling servers. Template-based modeling servers used were SWISS-MODEL (Waterhouse *et al.,* 2018) and whereas the comparative modeling-based server used was ROBETTA (Metaserver) (Kim *et al.,* 2004). Those sequences whose BLASTp results had query coverage (>80%) and identity (>30%) were modeled with the homology-based modeling server SWISS Model. *Insilico* modeling was done with the help of the *abinitio* based ROBETTA server for those targets that did not have any homologous sequences from BLASTp analysis. The percentidentity, maximum coverage, and similarity of 30-50 percent between the target and template sequences, as well as a Global Mean Quality Estimation (GMQE) near 1, were chosen as parameters in the SWISS-MODEL to ensure the quality of the modeled structures. XRN2 and FGB1 are among the targets that have been simulated usingthe SWISS-MODEL server. The ROBETTA server was used to estimate the structures of the target, FTF1**.**

Validation of protein structures. As backbone connectivity issues may lead to residual mistracings, residue misalignments or mis-registrations, side-chain misplacements, etc., *in-silico*-built models may contain improper bond connectivity and torsion angle. As a result of the same, atoms may be randomly positioned, which can be statistically differentiated or distinguished from the correct distributions. One approach used for this is the Ramachandran plot, which analyses peptide dihedral angles and returns residues that are beyond the energetically permissible ranges. The PROCHECK tool in SAVESv6.0 (Structural analysis and Verification server) was used to create the Ramachandran plot (SAVESv6.0 - Structure Validation Server (ucla.edu) (Laskowski *et al.,* 1993).

Visualization and Minimisation of energy of modeled targets. SWISS PDB Viewer was used for viewing and visualising the modeled structures in PDB format. Then, after choosing all of the residues, the "energy minimisation" option was selected from the tools menu for structural stabilization. The loops for those residues found in disallowed regions in the Ramachandran plot were then built.

Ligand preparation. The biomolecules cefazolin, succinic acid and furaneol were chosen for the analysis. Apart from these, tebuconazole was used as reference molecules to compare the efficacy of these selected

molecules. The ligand structures were downloaded in SDF format from the PubChem database.

Molecular Docking. Molecular docking is a modern bioinformatics approach that is mostly utilized to determine the mechanism of action of small compounds against possible protein targets in order to generate innovative therapeutic medicines for blocking or activating target proteins based on small molecule behavior. This is accomplished by placing small molecules in close proximity to potential protein targets and simulating their interactions with one another (Taylor *et al.*, 2002). Molecular docking can be used to virtual screen a large number of new small molecules, making structure-based drug design easier and screening time shorter (Amaro and Mulholland 2018; Gao *et al.*, 1998). Docking was used for investigating the binding affinities of proteins and biomolecules. PyRx 0.8, AutoDock Vina module was used to perform molecular docking. PyRx was used to convert targets into macromolecules of protein. Conjugate gradient, first-order derivatives of an optimization technique with 200 steps, and commercial molecular mechanics parameters-Unified Force Field were used to reduce all ligand structures (UFF). The Computed Atlas Topography of Proteins, CASTp 3.0 server was used to determine binding site pockets for the targets (Binkowski *et al.*, 2003). Ligands were able to generate flexible conformations and orientations with an exhaustiveness of 8 when using a rigid receptor. Biomolecules with less than -5 kcal/mol binding energy with higher number of targets were chosen.

Docked complex visualisation. BIOVIA discovery studio client 2021 was used to visualise the docked complex files. The software was used to access the modeled protein structure as well as the files acquired from docking of each ligand and associated protein, and ligand interactions were visualised and labelled after highlighting the ligand-binding site using the H-bond surface receptor. These files were saved as both discovery studio and picture files.

RESULTS AND DISCUSSION

Panama wilt even though reported in 1874 in Australia, emerged as a dreadful one in the 1950s where it became a menace for the “Gros Michael” banana cultivar plantations where it was grown as a mono-crop (Pleotz, 2015). Later on, the TR4 emerged as the most dreadful one which devastated the Cavendish cultivar that still dominates the world export market and is the only resistant cultivar to race 1 of the pathogen. With only a few methods to manage the disease that exists to date, there is a need for the continuous search for environment-friendly and practically feasible methods for the management.

Bacterial endophytes have been used in the biocontrol of many diseases of many important crops and they were found to be producing biomolecules during their interaction with the pathogen. So biomolecules produced by bacterial endophyte, *B. velezensis* YEBBR6 when dual cultured with *Foc* was subjected to molecular docking experiment to determine the effective ones with their mode of action and fungicidal effectiveness against potential virulent targets of *Foc*.

Modeling of proteins. G protein ß subunit (FGB1) was modeled using a template protein from PDB with ID 7CX2 that had a percentage identity of 52, a coverage of 94 percent, and a GMQE score of.83. The XRN2 was the second, with a template protein (PDB ID-3FQD) that had 51.57 percent identity, 84 percent coverage, and a GMQE score of 0.62 (Table 2). FTF1 (1079 residues) sequence was retrieved from UniProt and modeled using ROBETTA server with a confidence score of 0.36 **(**Table 3). Structures of the ligands and modeled protein targets are shown in Fig. 1.

Validation of models. The validity of the modelled structures was checked using a Ramachandran plot obtained from the PROCHECK program of the SAVES server. According to the Ramachandran Plot, the target protein FGB1 has 87.3 percent of its residues in the most favorable region, 12.6 per cent in the additional allowed region, and 0.3 per cent in the generously allowed zone **(**Fig. 2). XRN2 had 84.8, 13.7, and 1.5 per cent residues in the most favored, additional allowed, and generously allowed regions, respectively **(**Fig. 3). The percentage of Fusarium transcription factor 1 target protein residues that fell within the most favoured region, additionally allowed region and generously allowed region, respectively, was 83.3, 15.2, and 1.5 per cent **(**Fig. 4).

Docking

Cefazolin. Cefazolin was found to effectively inhibit the function of all the targets as they were having more affinity towards them, which was greater than tebuconazole (Fig. 5). Cefazolin had a binding affinity of -9.5 kcal/mol with XRN2 (H bonds- ALA A:110, ASP A:351, MET A:1, VAL A:348), -9.6 kcal/mol with FGB1 (H- bonds; ARG C: 167, TYR C: 75, GLN C: 251) and -6.6 kcal/mol with FTF1 (H-bonds; LEU A:570, CYS A:574) (Table 4) (Fig. 6**)**. Greater affinity for XRN2 will impair the pathogen's normal mRNA turnover. 5´ → 3´ Exoribonuclease 2 uses divalent cations as cofactors to remove nucleoside monophosphates from 5'-monophosphorylated RNA (Jinek *et al.*, 2012). As a result, the pathogen's regular functioning and survival are jeopardized. XRN2 contributes to the processing of non-coding RNAs such as rRNA precursors (Geerling *et al.*, 2000), the generation of snoRNAs (Petfalski *et al.*, 1998), and the elimination of hypomodified tRNAs and helps in the proper functioning of translational machinery (Miki *et al.*, 2013). In yeast, XRN2 is reported to be involved in breaking down the telomeric repeat-containing RNA (TERRA) whose accumulation will inhibit the activity of telomerase. Hence it is necessary for conserving the integrity of chromosomes as well as the length of telomere (Wang *et al.*, 2015). As a result, the pathogen's regular growth and survival is harmed. Membrane protein, FGB1 (*Fusarium* Guanine Binding protein) is engaged in the signal transduction pathway that regulates biological processes. The activation of transmembrane receptors by effect or molecules is mediated by G protein subunits. This regulates gene expression, cellular function, metabolism, and blocking of the target (Gilman, 1987). Apart from these, FGB1

also influences cell differentiation, proliferation, pathogenicity, heat resistance, and germination percentage (Herbert and Mars 1990). In fungi, G protein signaling is supposed to be mediating processes like growth, maturation, and virulence (Lengeler *et al.*, 2000). It has been suggested that fusarium transcription factor 1 (FTF1) is involved in the proliferation of fungi, as well as their maturation and the progression of the disease. In addition, they regulate the sexual and asexual development of the fungus (Jiang *et al.*, 2011). So the binding affinity of cefazolin to the target FTF1 suggests that all the mentioned functions will be interrupted in the fungus. Similary, the active components of olive leaf extracts, thyme essential oil, and *Boswellia carteri* (Olibanum) essential oil were used to dock with 11 distinct protein targets of *Fusarium oxysporum* f sp. *lactucae* (FOL), which causes wilt in lettuce. Compounds such as carvacrol, -thujene, and thymol were discovered to have stronger affinity to the targets examined. The maximum binding affinity was shown by the carvacrol ligand, and it was also for the protein Hog1 (Omar *et al.*, 2021). Six compunds derived from *Cyamopsis tetragonoloba* leaves and fruits were docked against the fungal protein targets lanosterol 14-demethylase of the pathogenic fungi *Rhizoctonia solani* and *Drechslera oryzae*. The target protein was most closely bound to stigmasterol and sitosterol (Sumeethsingh *et al.*, 2022). In this study, cefazolin was having higher affinity towards the targets. Still these results need to be validated through the wet lab as well as field-level studies.

Table 1: Details of selected protein targets.

Sr. No.	Name Of The Target	Role of the Target	Uniprot ID	Reference
1.	FGB (G-protein-β-subunit)	Regulation of development and pathogenicity in Fusarium	Q96VA6	Soundaryarajan *et al*. (2011)
2.	XRN2	RNA degradation	A0A559KT57	Maldonado Bonilla *et al.* (2018)
3.	FTF1	Development, growth and pathogenesis	Q2V9X3	Ghag *et al.* (2014)

Table 2: Details of protein targets modeled by SWISS Model.

Sr. No.	Uniprot Id	Protein Target Name & Length	Template Protein PDB Id	Sequence Identity %	Sequence Similarity %	Coverage %	GMQE
1.	A0A559KT57	XRN2 988	3fqd.1.A	51.57	44	84	0.62
2.	Q96VA6	FGB 394	7cx2	54.96	52	94	0.83

Table 3: Details of protein targets modeled by ROBETTA.

Uniprot Id	Protein Target Name & Length	Domain Id	Confidence Score %
Q2V9X3	FTF1 1079	143726	0.36

Table 4: Details of molecular docking analysis.

	Binding affinity (kcal/mol) of small on different targets				H-bonds formed			
	Cefazolin	Furaneol	Succinic acid	Tebuconazole	Cefazolin	Furaneol	Succinic acid	Tebuconazole
XRN2	-9.5	-5.6	-4.8	-8.1	ALA A:110 ASP A:351 MET A:1 VAL A:348	ALA A:110	TYR A:616 TYR A:618	ALA A:110 ASP A:351 TYR A:616
FGB1	-9.6	-4.6	-4.2	-8.5	ARG C: 167 TYR C 75 GLN C 251	ARG C: 332	SER C:206 VAL C: 294 ILE C:250 ARG C: 167 ILE C:207	SER C:206 VAL C:294
FTF1	-6.6	-4	-3.8	-6.3	LEU A:570, CYS A:574	SER A:646	ARG A:664 ARG A:671	GLY A:573

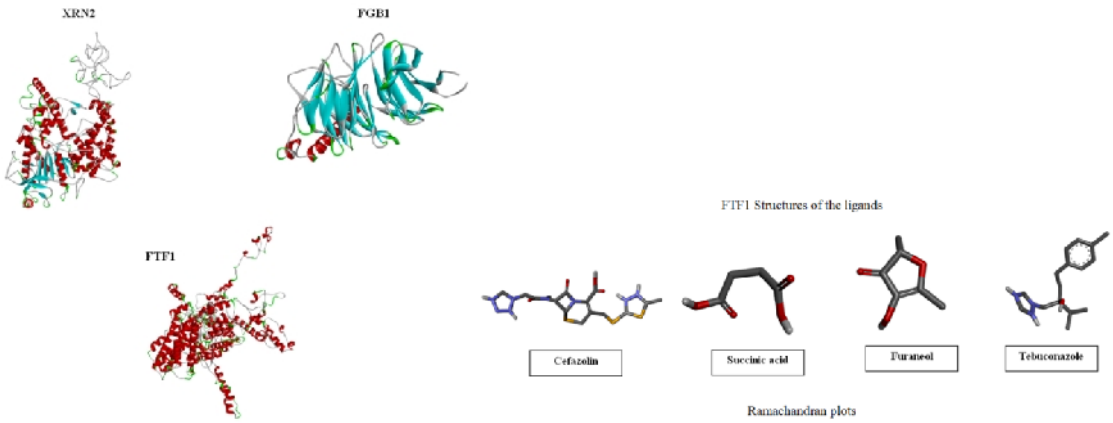


Fig. 1. Structures of modeled targets XRN2, FGB1 and FTF1.

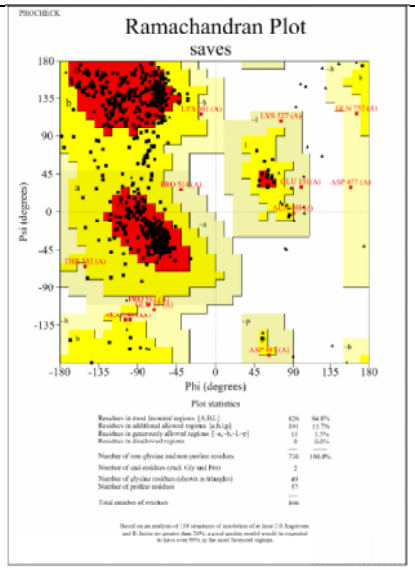


Fig. 2. XRN2.

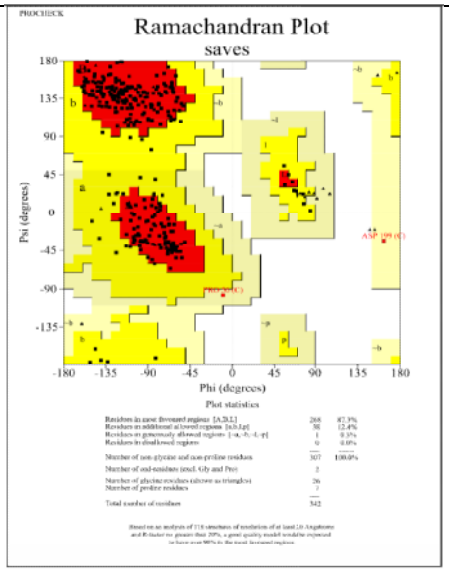


Fig. 3. FGB1.

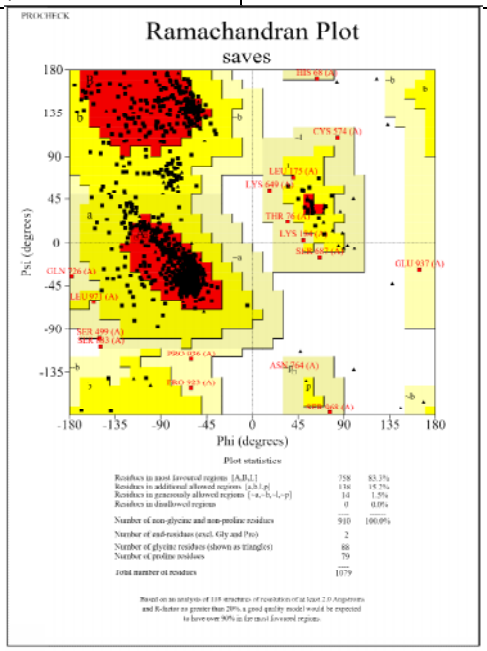
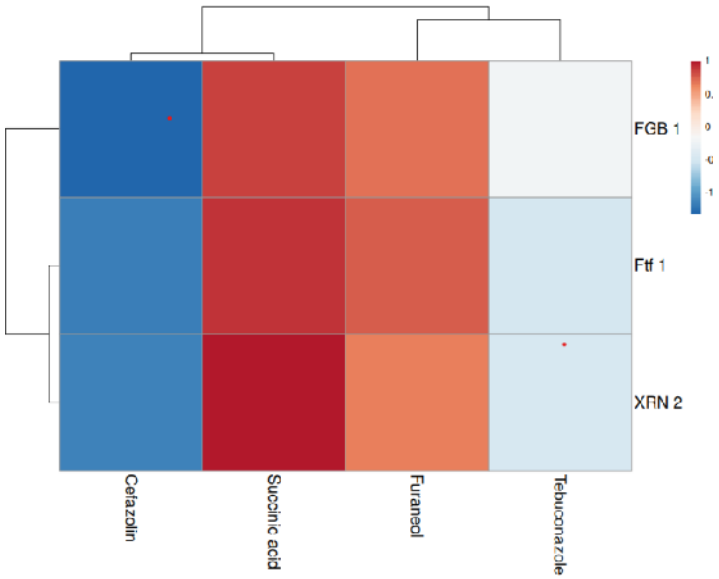
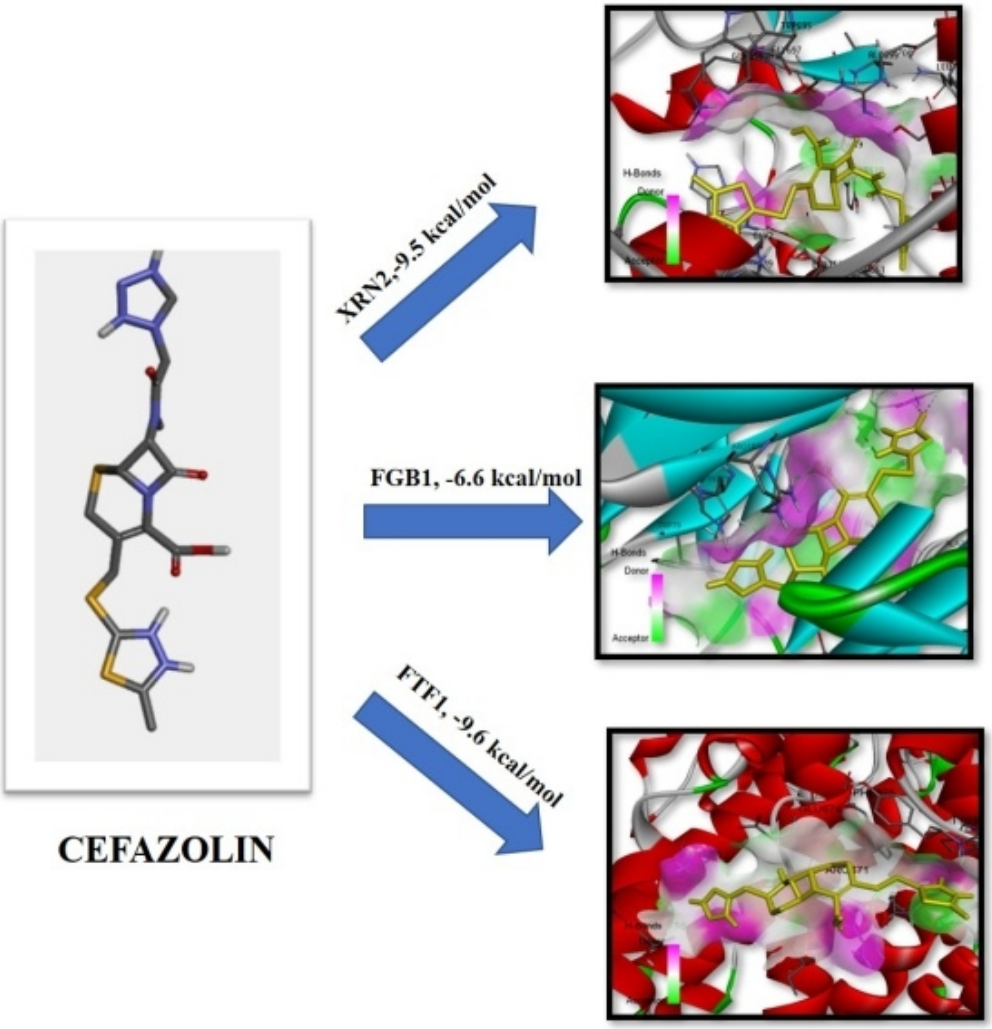


Fig. 4. FTF1.

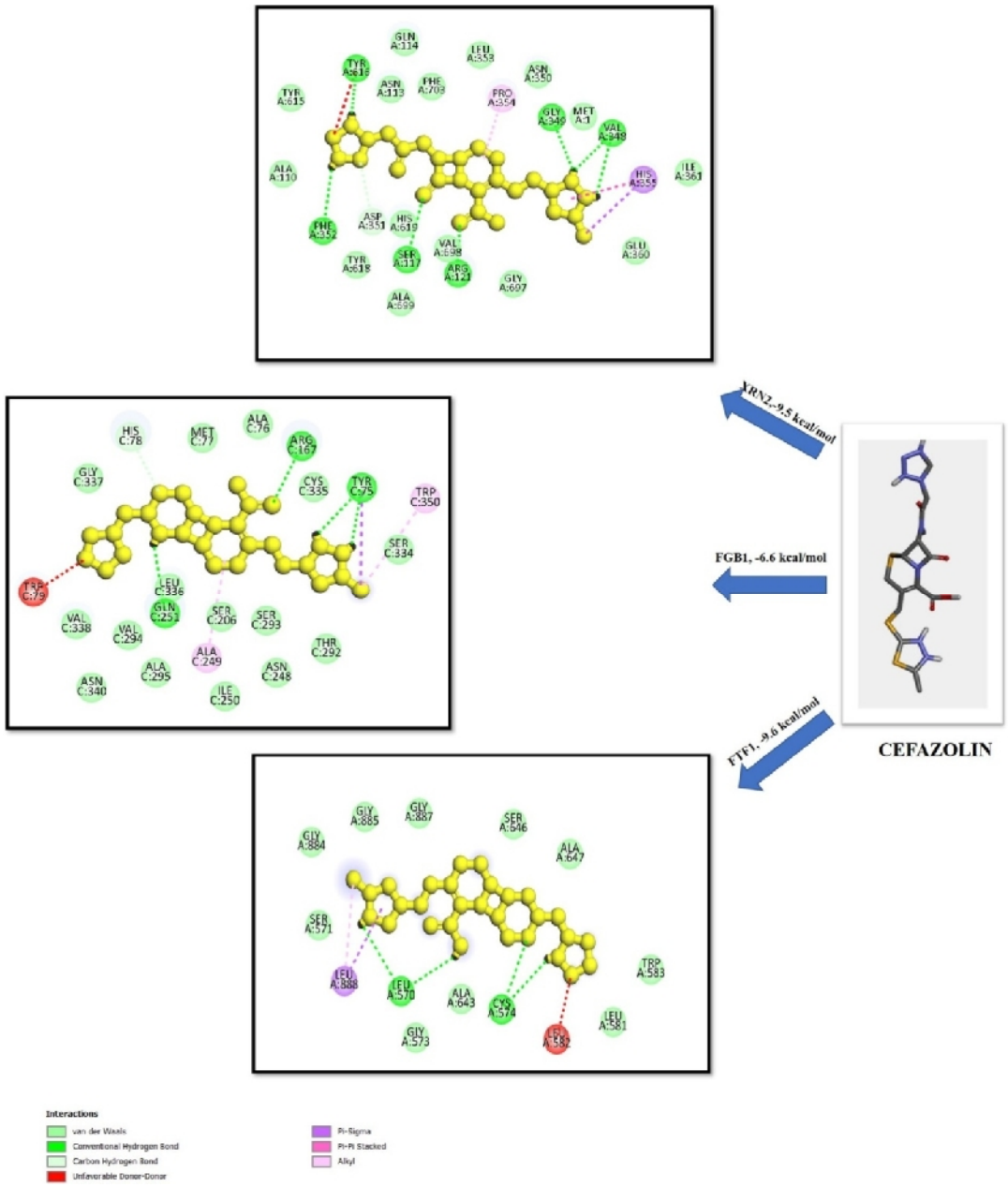


*More negative the binding energy, more is the binding affinity of the compound with the target

Fig. 5. Heat map depicting the binding energies of the compounds screened with different targets.



Docked complexes -targets and cefazolin



2D interaction images of docked complexes

Fig. 6. Docking complexes- targets with the compound cefazolin and interactions between them.

CONCLUSION

Computational modeling of the protein targets of *Foc* and docking of the same with the biomolecules produced by *Foc* antagonistic bacterial endophyte, *B. velezensis* YEBBR6 led to the unraveling of antifungal activity of biomolecule, cefazoline. The higher binding affinity towards the targets XRN2, FGB1 and FTF1indicates their ability to impede the functions of the targets and in turn affect the normal growth, proliferation, and virulence of *Foc.* Hence the *in-silico* analysis suggests that cefazoline can be explored for its antimycotic activity towards *Foc.*

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Conflict of Interest. None.

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