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In-Silico Validation of *Prosopis ciniraria* Therapeutic Peptides Against Fungal Cell Wall: Better Treatment Strategy for Fungal Diseases

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Abstract

Prosopis cineraria commonly known as Druce are valuable herb that holds antibacterial role, antifungal properties. We identified different peptides from this plant by deploying CADD (Computer-aided-drug-designing) approaches, these peptide sequences are as follows seq1 (RHDEEEEKAKV),seq3(KSNSTVEISQNVQSVDSSKM),seq4(KQVAEMNKPAVGSKTS DANHDLKS),seq5(KTKSAGNDSIQSTKPVPSALTVDKA),seq6(RELEDSNIHHVAASVVLESKSSRT), and seq8(LYSK VELHPFGLHNLGNSCYANAVFSV), these peptides holds therapeutic properties as shows interaction with chitin, a major constituent of fungal cell wall. Molecular docking was conducted by using AutoDock-Vina tool and the results were found to be promising where all binding energies were found in the range of − 9.1 to − 7.5 kcal/mol, it indicates strong binding of peptide sequences with chitin molecule. Even the toxicity analysis supports the considered peptide sequences to hold therapeutic role against fungus with non-toxic effect on humans. These peptides were successfully predicted as important therapeutic agents of *P. cineraria*seed that can initiate chitin breakdown, due to their possible strong interaction with fungal cell wall and it also suggests this medicinal plant holds the key for multiple fungal disease treatments. This study will open new research dimensions and integration of computational biology with microbial pathology that will assist scientific and medical community to develop rapid disease prevention strategies against fungal pathogenesis.

Keywords *Prosopis cineraria* seed · Molecular docking · Chitin · Peptide sequences · Computational biology

Introduction

Prosopiscineraria (L.) Druce is a valuable herbal plant that has been described by ancient texts. It belongs to family Fabaceae, and holds antibacterial role, antifungal properties and antioxidants; this plant shows multiple therapeutic roles as also involved in wound healing and antifungal role (Napar et al. 2012; Nagori 2011). It has historically can be used to manage pain such as leprosy, typhoid, diabetes, leucoderma, dyspepsia, including allergic reaction (Garg and Mittal et al. 2013). Tannins (gallic acid), steroids (Stigmasterol, campesterol, sitosterol, etc.), Flavone compounds (Prosogerin A, B, C, D, and E), alkaloids (Spicigerine, Prosophylline), and other metabolites were being extracted from the tree. Such chemicals may cause Nuclear_factor_KappaB from reaching the nucleus, preventing the overproduction of proinflammatory cytokines but instead acting as a cure for Lipopolysaccharide-induced cellular harm (Sharma and Sharma et al. 2020). In our recent studies we identified proteins of this plant can inhibit growth of fungus in culture environment, the MALDI-ToF MS/MS experiments revealed 15 peptides that may act as potential fungal attack agents or holds therapeutic properties (Solanki et al. 2018). In one of the previous studies, it was shown that extract of *Prosopis cineraria* inhibits DPP-4 (Dipeptidyl peptidase) as well as cholinesterase enzyme, which makes it suitable for treatment of Diabetes and neurological disorders (Ram et al. 2019). In another recent study it was shown that the extracts of this plant hold antibacterial property against many bacterial species like *Staphylocuccus aurius* (Neghabi-Hajiagha et al. 2016).Our current work is extension of our previous study, and here we conducted

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successful molecular docking and simulation experiments to reveal interaction of these peptides with chitin, to reveal role of *Prosopis cineraria*seed in breakdown of fungal cell wall.Immune—competent people, unlike immunocompromised people, are protected from fungal infections by their functioning innate immune system, which identifies and destroys fungal invaders quickly. In one of the recent study it was found that *Prosopis juliflora* extract holds ant-microbial properties against food spoiling microbes (Saleh and Abu-Dieyeh 2021). It has been also noted that *Prosopis cineraria* extracts embedded and transferred with nano-particle delivery system shows greater success in cancer treatments (Jinu et al. 2017). The immune system's recognition of fungal cellular characteristics appears to be a critical component of human antifungal defense. Dectin-1, for example, recognizesβ-glucan on the fungal cell wall as a pathogen-associated molecular pattern (PAMP) and triggers pro- and anti-inflammatory cytokines through a myeloid-differentiation-primary-response-gene-88 (MYD88-) dependent signaling cascade. Humans do not biosynthesize chitin, but they do have chitin-degrading enzymes called chitinases. Chitotriosidase (CHIT-1) and acidic mammalian chitinase (AMCase) are two known human chitinases with chitinolytic activity, as well as a number of noncatalytically active chitinases known as chi-lectins. CHIT-1 and AMCase have unclear roles, although they are considered to help in the defence against chitin-containing infections. Serum chitotriosidase levels in guinea pigs, for example, rise in response to systemic fungal infection. The fact that chitinase levels change in response to fungal infections implies that chitinase reactions in the host might be used as a diagnostic (Vega and Kalkum 2012). Our study suggests targeting chitin cell wall of infectious fungus could be possible in all individuals with the help of therapeutic peptides that were isolated from *Prosopis spp.* Seeds. Figure 1 indicates general workflow of current in-silico study, that clearly show peptides of *Prosopis cineraria* interacts with chitin by deploying molecular docking and MD simulations. This study will open new dimensions in developing regimens against fungal infections.

Methodology

Peptide Sequence Data Collection

Sequence based data for all peptides of *P. cineraria* seedswere obtained from our previous MALDI-TOF MS/MS analysis of its protein extracts (Solanki et al. 2018). Chitin structure was downloaded from PubChem database in sdf format, which was converted to pdb format after using openbabel tool (O'Boyle et al. 2011).

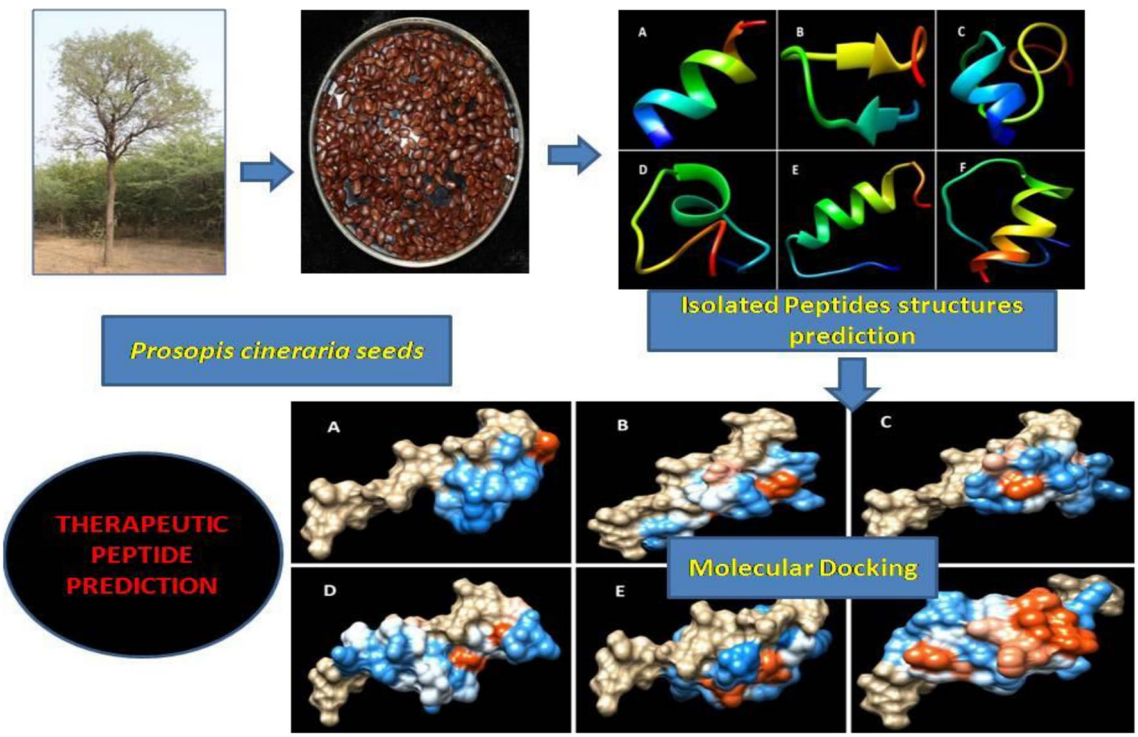

Fig. 1 Workflow for determining *Prosopis cineraria* peptides interaction with chitin

Peptides Structural Designing

Peptide's structure was designed by using PepFold 3.5 server (Thévenet et al. 2012), which allows *ab-initio* prediction of structures and follows hidden marlov model probability algorithms to produce refine structures for given sequences. All structures were validated by proSA webserver (Wiederstein and Sippl. 2007), this tool assist in determining Z-scores for all protein structures.

Toxicity, Allergenicity Predictions of Peptides

ToxinPred tool (Gupta et al. 2013) was used to check the toxicity of peptides on the basis of SVM scores; also Allergen-FPtool (Dimitrov et al. 2014) was deployed to predict the allergenicity of these *P.cineraria* seeds peptides. Other biochemical parameters like GRAVY score, Instability index, pI, and Half-life was calculated by subjecting these peptide sequences to ProtParam (Garg et al. 2016) server, these all filters assisted in finalizing sequences from our 15 sequences.

Molecular Interaction Studies Between Chitin and Peptide Sequences

The study of the interactions between the protein and the ligand is known as docking. Ionic contacts, hydrogen bonds, and van der Waals interactions are some of the many forms of protein–ligand associations (Pantsar and Poso, 2018). The total of all molecular interactions between the ligands and the receptor is the binding free energy. The scoring function used to estimate the binding capacity of both the ligands and the receptor once docked is known as Docking Score (Adibpour et al. 2012; Gilad and Senderowitz. 2014). Docking studies were conducted by using AutoDock vina (Trott and Olson 2010) software, for each considered sequences that were docked against chitin molecule. The resulted complexes binding energies was calculated by using this software, also PyMOL software (DeLano and Bromberg 2004) was deployed for visualization of final docked complexes.

Molecular Dynamics Simulation

Molecular dynamic simulations were conducted by using iMODStool (López-Blanco et al., 2014) to reveal eigen value plots, that clearly indicates stability of docked complexes along the trajectory during simulation analysis for default time span. Here variance plots and eigen value plots were calculated for docked complexes to indicate stable interaction between selected peptide sequences and chitin molecule. Further GROMACS tool (Van Der Spoel et al. 2005) was deployed for molecular dynamics and simulation studies for all the subjected complexes to all atom OPLS force field, trajectory analysis was conducted for 50 ns time span, which assisted in generating RMSD and RMSF plots indicating inference about stability of interaction between peptide sequences and chitin. The NVT and NPT ensembles were used to accomplish equilibration in two phases (constant number of particles, volume, and temperature at 50 ns). Following the equilibration phase, the Particle-Mesh Ewald summation technique (Shan et al. 2005) was used, followed by a 20-ns production phase. GROMACS' g rms and g rmsf tools were used to examine the generated trajectories.

Results

Structural Predictions of Peptides

15 peptides sequences were obtained from seeds of *P. cineraria* by using of MALDI TOF MS/MS were considered for structural predictions. Structures of *P. cineraria* peptides was predicted successfully by deploying PepFold3.5 tool, and then all structures were also validated on the basis of overall model quality and knowledge-based energy analysis in proSA server, that resulted z-scores in suitable range of -5 to $+5$. The z- cores for finalized sequences are as follows: Seq1 z score: -1.44, seq3 z score: 0.48, seq4 z score: -0.72, seq5 z score: 0.18, seq6 z score: 0.02, and seq8zscore: -2.34. All the structures were visualized in Pymol software and are presented in Fig. 2.

Toxicity, Allergenicity Predictions

Peptide analysis report generated for allergenicity (Table1), so that only non-allergen peptides could be selected for revealing therapeutic relevance in human fungal treatment strategy development. ProtParam analysis report for 15 peptides assisted in checking stability parameter, out of these 15 peptides only 8 peptides were found to be stable as well as non-allergen. Toxicity analysis reveals that only 6 peptides were non-toxic out of 8 peptides (Table2), and then these structures were subjected for docking to chitin molecule, PubChem CID: 24,978,517: Molecular Formula: $C_{64}H_{106}N_8O_{41}$.

Docking Analysis of Peptides with Chitin

Molecular docking was performed by deploying AutoDockVinatool, which assisted in determining binding energy (Table3) and revealing proper binding pockets (Fig. 3) where enzymatic activity of these peptides occur. These amino residue's R_groupslike in glutamic acid (Glu) as well as aspartate (Asp) have also been discovered to be essential for these considered peptides' action. Glu functions as a hydrogen donor towards the glycosidic

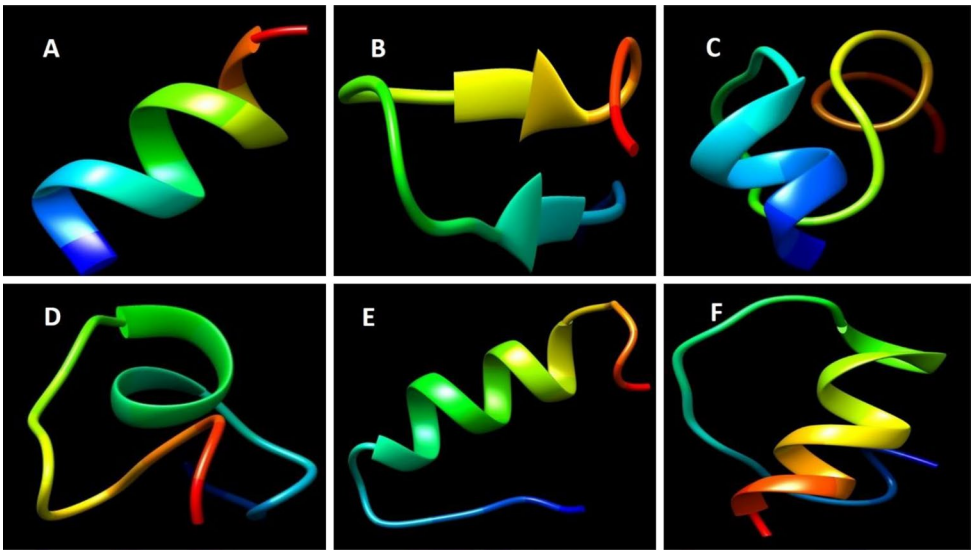

Fig. 2 Predicted Structures for selected sequence: **A** Seq1; **B** Seq3; **C** Seq4; **D** Seq5; **E** Seq6; **F** Seq8

Table 1 *P.cineraria* seed peptides analysis report of ProtParam tool (Ex-pasy server) and AllergenFP tool

Peptides sequence (MALDI-TOF)	Mol.wt\ (MALDI-TOF)	Allergenicity (AllergenFP)	pI	GRAVY	Instability index	Half-life (h)
KAKVGRA	529.3336	(Allergen)	11.17	−0.7 (Hydrophobic)	52.69 (Unstable)	1.3
KEHQRA	568.2717	(Allergen)	8.75	−2.8 (Hydrophobic)	64.23 (Unstable)	1.3
KENASVGVKQ	802.4185	(Allergen)	8.59	−0.93 (Hydrophobic)	21.31 (Stable)	1.3
KVADSLPDRS	871.4399	(Allergen)	5.96	−0.88 (Hydrophobic)	59.49 (Unstable)	1.3
RTPIHVELERS	1092.5927	(Allergen)	6.76	−0.891 (Hydrophobic)	60.25 (Unstable)	1
RHDEEEEKAKV	1113.4938	(Non-Allergen)	4.96	−2.455 (Hydrophobic)	27.79 (Stable)	1
RSSFVNKEFCNHSKE	1582.7198	(Non-Allergen)	8.21	−1.307 (Hydrophobic)	37.25 (Stable)	1
KSNSTVEISQNVQSVDSSKM	1907.9072	(Non Allergen)	6.07	−0.76 (Hydrophobic)	42.78 (Stable)	1
KDECHPPSVNTRHDEEEEA	2206.9185	(Allergen)	4.48	−2.053 (Hydrophobic)	125.66 (Unstable)	1.3
KQVAEMNKPAVGSKTSDANHDLKS	2339.1539	(Non Allergen)	8.44	−1.058 (Hydrophobic)	23.98 (Stable)	1.3
KTKSAGNDSIQSTKPVPSALTVDKA	2343.2282	(Non Allergen)	9.53	−0.656 (Hydrophobic)	42.17 (Stable)	1.3
RELEDSNIHHVAASVVLESKSSRT	2406.2139	(Non Allergen)	6.03	−0.550 (Hydrophobic)	33.16 (Stable)	1
MTSVCSSCCSFKCQIAHWRQ	2419.9953	(Non Allergen)	8.52	0.090 (Hydrophilic)	26.65 (stable)	30
KSAGNDSIQSTKPVPSALTVDKATSVRGK	2628.3719	(Allergen)	10	−0.617 (Hydrophobic)	51.88 (Unstable)	1.3
LYSKVELHPFGLHNLGNSCYANAVFSV	3035.4964	(Non Allergen)	6.91	0.289 (Hydrophilic)	39.02 (Stable)	5.5

link, slicing the substrate's C-O bond, while Asp functions like a nucleophile to form a glycosyl peptide intermediate. The Glu combines with water to make hydroxyl ion, a greater nucleophile to water, that targets the glycosyl peptide intermediates to produce the breakdown product while keeping overall peptides intact, these peptides behave very similar to lysozyme enzymatic actions. Many of the amino R-groups inside these peptide sequences can behave as nucleophiles and are commonly mentioned in the active site of enzymes. Cysteine, Serine, Threonine, Tyrosine, Glutamic Acid, Aspartic Acid, Lysine, Arginine, and Histidine are some of these amino acids. Therefore, all selected 6 peptide sequences like seq1, seq3, seq4, seq5, seq6, and seq8 follows this mechanism to cleave chitin apart and hence leads to breakdown of chitin cell wall of fungal pathogens.

Table 2 Toxicity results for *P. cineraria seed*peptides (ToxinPred analysis report)

Peptide ID	Peptide Sequence	SVM Score	Prediction	Hydrophobicity	Hydropathicity	Hydrophilicity	Charge	Mol wt
seq1	RHDEEEEKAKV	−0.71	Non-Toxin	−0.62	−2.45	1.95	−1.50	1369.60
seq2	RSSFVNKEFCNHSKE	0.18	Toxin	−0.39	−1.31	0.55	1.50	1812.19
seq3	KSNSTVEISQNVQSVDSSKM	−0.63	Non-Toxin	−0.27	−0.77	0.33	0.00	2168.65
seq4	KQVAEMNKPAVGSKTSDAN-HDLKS	−0.78	Non-Toxin	−0.29	−1.06	0.58	1.50	2556.19
seq5	KTKSAGNDSIQSTKPVPSAL-TVDKA	−1.66	Non-Toxin	−0.23	−0.66	0.41	2.00	2544.21
seq6	RELEDSNIHHVAASV-VLESKSSRT	−1.16	Non-Toxin	−0.26	−0.55	0.43	0.00	2665.26
seq7	MTSVCSSCCSFKCQIAHWRQ	1.28	Toxin	−0.15	0.09	−0.42	2.50	2305.98
seq8	LYSKVELHPFGLHNLGNSCYA-NAVFSV	−0.54	Non-Toxin	0.02	0.29	−0.62	1.00	2980.80

Table 3 Docking results for sequences with chitin

Sr.No	Docked Complex	Binding energy (Kcal/mol)
1	Seq1-chitin	−8.5
2	Seq3-chitin	−7.7
3	Seq4-chitin	−8.0
4	Seq5-chitin	−7.5
5	Seq6-chitin	−9.1
6	Seq8-chitin	−7.8

Molecular Dynamics and Simulation analysis

MD simulations were conducted on the basis of normal mode criteria by deploying iMODs tool, here eigen value plot (Fig. 4) indicates deformity associated during simulations of docked complexes; lower the value more deformation in structure, as this value is in direct relation with energy associated for bringing deformity in structure. Also, variance plot was obtained for docked models, as the value of variance is inversely proportional to eigen values (Fig. 5). Here all docked complexes have stable patterns and therefore it indicates perfect docking between peptide sequences and chitin molecule. RMSD (Fig. 6) and RMSF (Fig. 7) plots clear the picture about interaction patterns between all 6 selected peptide sequences with chitin molecule, as here we also used reference molecule (PDB ID: 2D49; Chitinase and

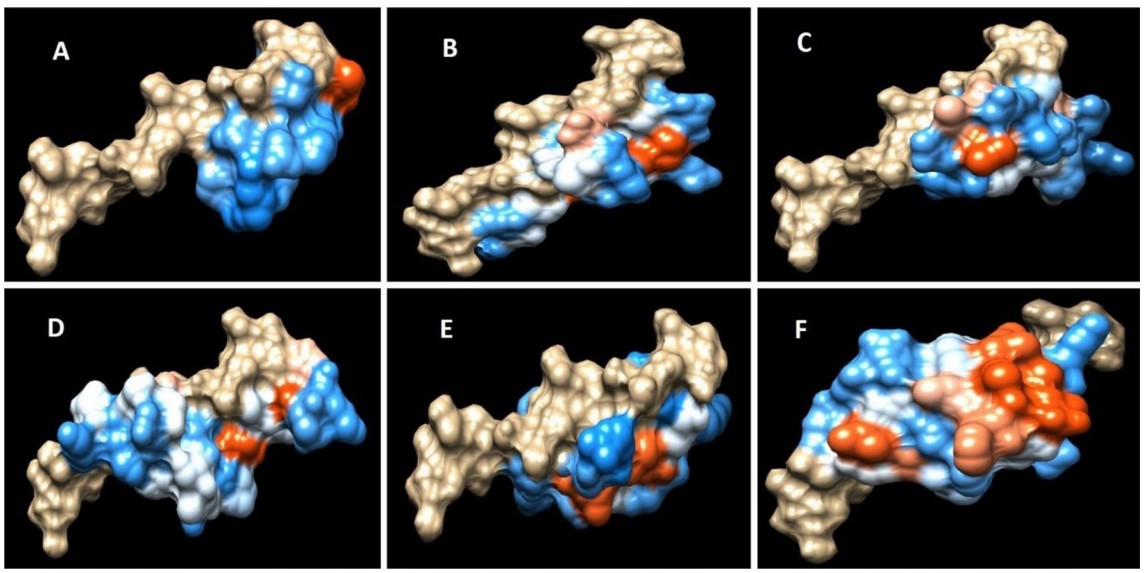

Fig. 3 Docked complexes: **A** Seq1-chitin **B** Seq3-chitin **C** Seq4-chitin **D** Seq5-chitin **E** Seq6-chitin **F** Seq8-chitin

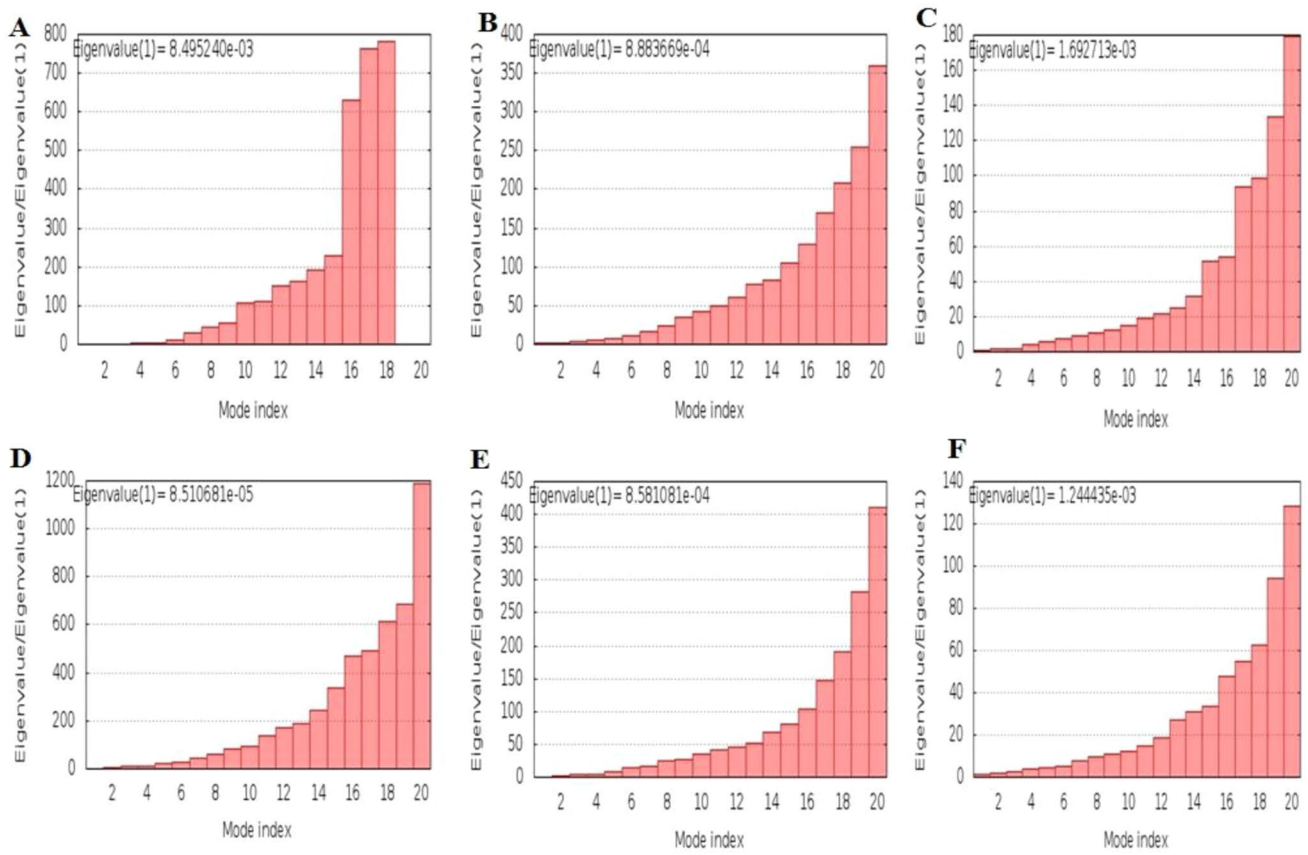

Fig. 4 Eigen-Value plot for docked complexes: **A** Seq1-chitin **B** Seq3-chitin **C** Seq4-chitin **D** Seq5-chitin **E** Seq6-chitin **F** Seq8-chitin

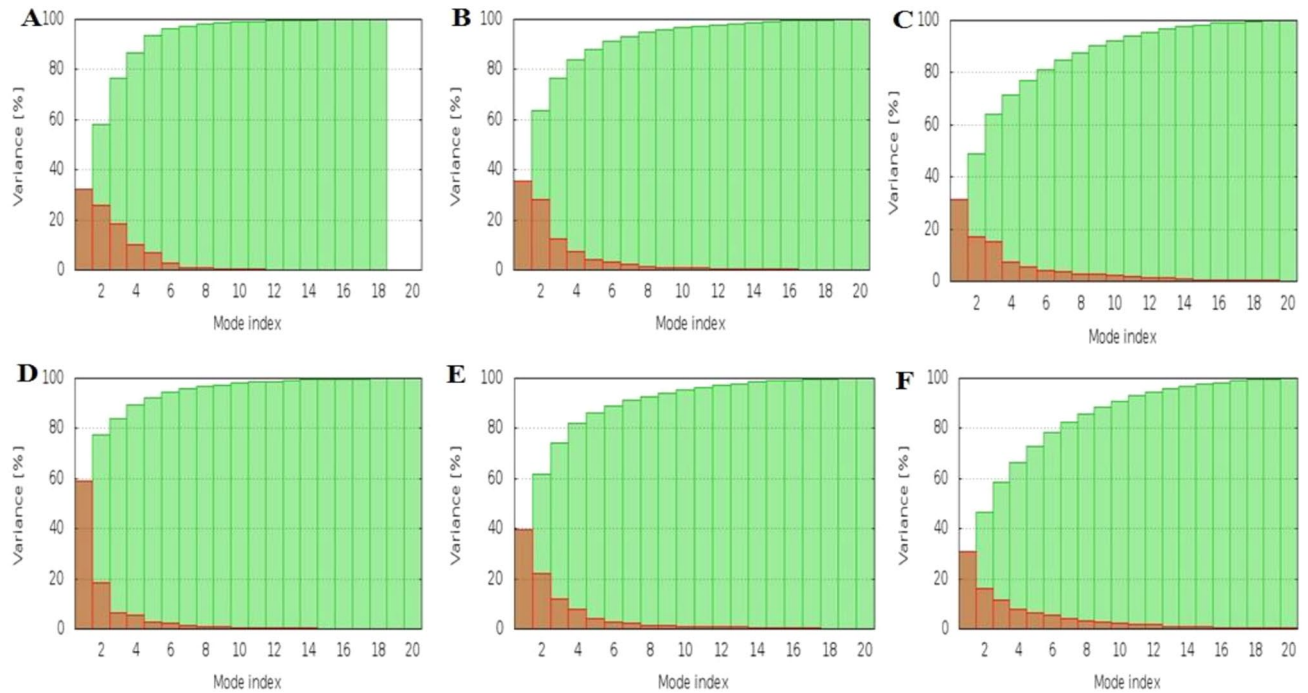

Fig. 5 Variance plot for docked complexes: **A** Seq1-chitin **B** Seq3-chitin **C** Seq4-chitin **D** Seq5-chitin **E** Seq6-chitin **F** Seq8-chitin

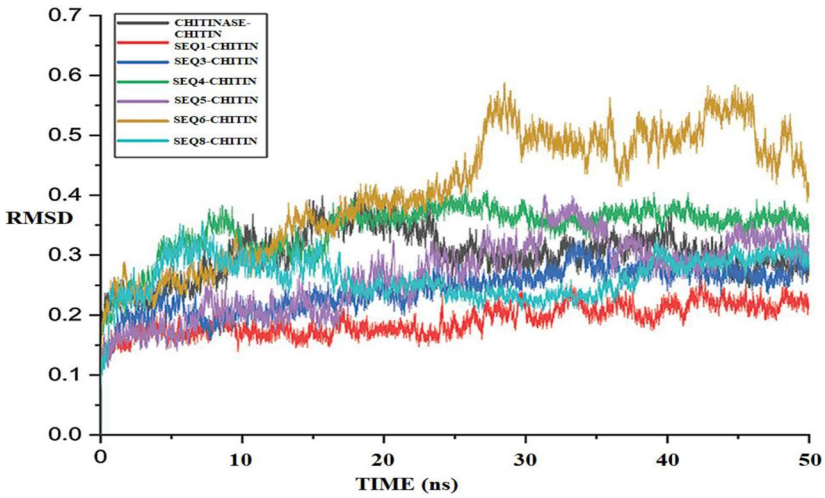

Fig. 6 Root mean square deviation plot for all 6 complexes and reference chitinase-chitin complex

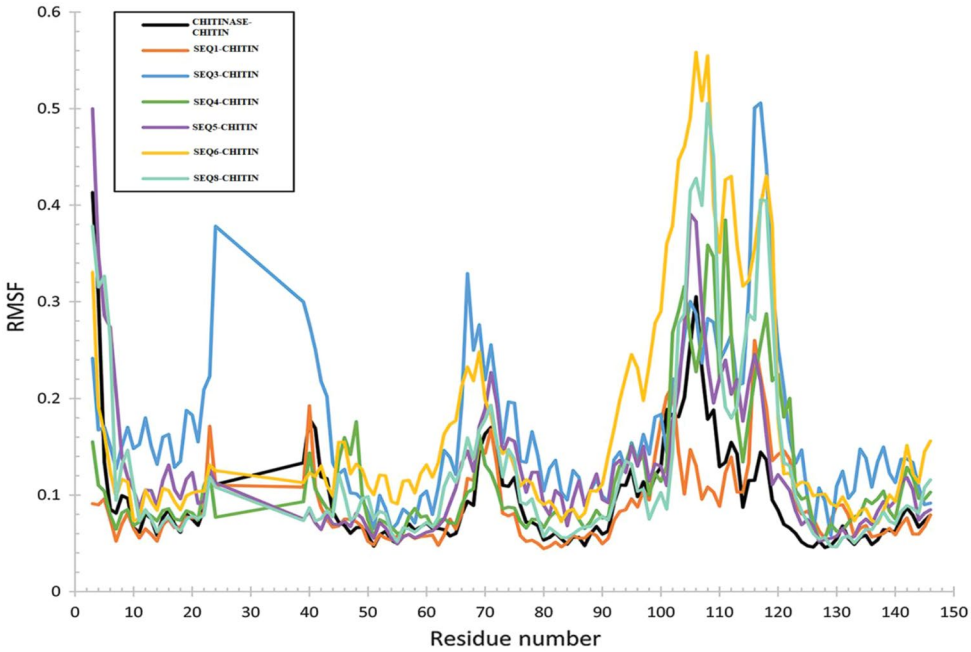

Fig. 7 Root mean square fluctuation plot for all 6 complexes and reference chitinase-chitin complex

chitin complex crystal structure retrieved from RCSB-PDB website) considered for comparative analysis. MD simulation indicates there is less deviation even after 50 ns time span. Interaction snapshots (Fig. 8) after simulation clearly indicates stable binding of peptides to chitin molecule.

Discussion

CADD (Computer-aided-drug-designing) approaches in therapeutic predictions revealed seq1(RHDEEEEKAKV), seq3(KSNSTVEISQNVQSVDSSKM),seq4(KQVAEMNKPAVGSKTSDANHDLKS),seq5(KTKSAGNDSIQSTKPVPSALTVDKA),seq6(RELEDSNIHHVAASVVLESKSSRT), and seq8(LYSKVELHPFGLHNLGNSCYANAVFSV), shows interaction with chitin, a major constituent of fungal cell wall.A CADD study was also found successful in many recent studies, where plant constituents were found to be effective against Sars-Cov2 (Joshi et al. 2020).*P. cineraria*was recently found to have one important chemical constituent vitexin that plays major role in inducing apoptosis of leukemia cells (Sarkar et al. 2021). In one of the previous studies, it was shown that extract of *Prosopis cineraria* inhibits DPP-4 (Dipeptidyl peptidase) as well as cholinesterase enzyme, which makes it suitable for treatment of Diabetes and neurological disorders (Ram et al. 2019). In another recent study it was shown that the extracts of this plant hold antibacterial property

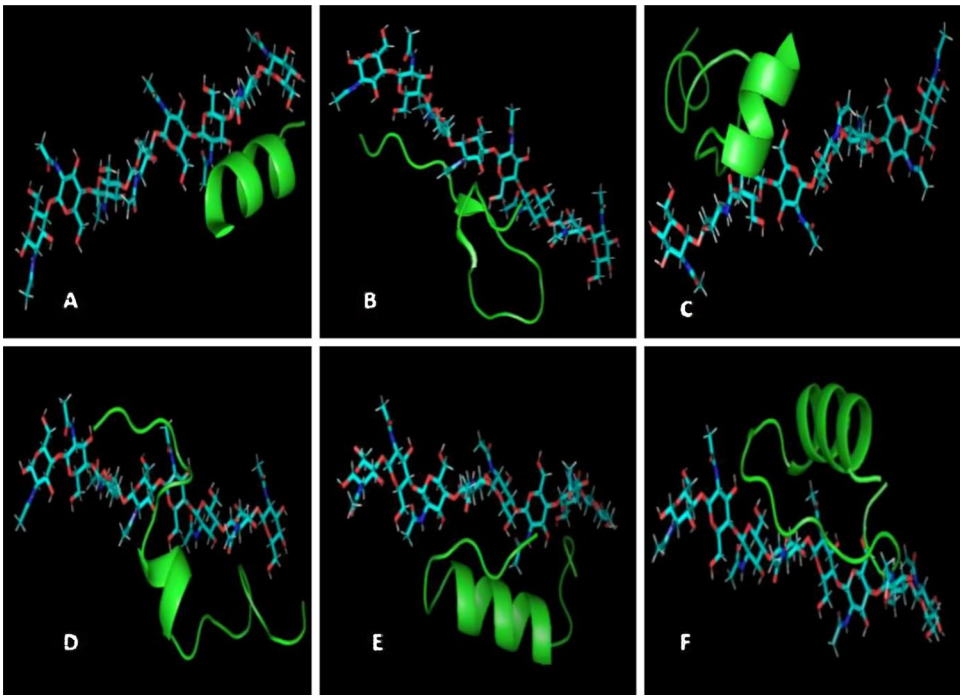

Fig. 8 Interaction patterns of various peptide sequences with chitin: **A** Seq1-chitin **B** Seq3-chitin **C** Seq4-chitin **D** Seq5-chitin **E** Seq6-chitin **F** Seq8-chitin

against many bacterial species like *Staphylocuccusaurius* (Neghabi-Hajiagha et al. 2016).In our recent studies we identified proteins of this plant can inhibit growth of fungus in culture environment, the MALDI-Tof experiments revealed 15 peptides that may act as potential fungal attack agents or holds therapeutic properties (Solanki et al. 2018), in current study we extended this work by deploying CADD approach for revealing therapeutic peptides interaction pattern against fungal cell wall.Here we clearly found the best docking scores in more negative to—4.0 kcal/mol range of binding energy that shows strong binding between peptide sequences and chitin (fungal cell wall compound). In one of our recent studies, we also find out that peptides from Dengue virus (Krishnan et al. 2020, 2021), *Troperymawhipplei* (Joshi and Kaushik 2021), Candida fungus (Akhtar et al. 2021a, b), Nervous Necrosis Virus (Joshi et al. 2021), and Human cytomegalovirus (Akhtar et al. 2021a, b) could be immunogenic for humans, in general by deploying molecular docking and simulation studies. Even the toxicity analysis supports the considered peptide sequences to hold therapeutic role against fungus with non-toxic effect on humans. These peptides were successfully predicted as important therapeutic agents of *Prosopis cineraria* that can initiate chitin breakdown, due to their possible strong interaction with fungal cell wall and it also suggests this medicinal plant holds the key for multiple fungal disease treatments.

Conclusion

Our research shows peptides of *Prosopis cineraria*seed holds good therapeutic potential against fungal pathogens as these peptides are involved in breaking chitin cell wall and leading fungal cells to face oxidative burst. Here we used bioinformatic tools that establish rapid screening of peptides in an efficient manner in terms of money as well as time. As there are large diverse fungi associated diseases, these Antifungal peptides can be used to treat fungal infections, as this study creates new research avenues for future wet-lab analysis of such useful therapeutic peptides. This study will open new research dimensions and integration of computational biology with microbial pathology that will assist scientific and medical community to develop rapid disease prevention strategies against fungal pathogenesis.

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Author Contribution PG and JS have prepared the framework of the study, AJ, VK, DSS, conducted the computational work and manuscript preparation. All authors have proofread manuscript.

Declarations

Conflict of interest All authors have no conflict of interest.

Ethical approval Not applicable, as it is in-silico work.

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