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Molecular Modelling and Insilico Engineering of PapMV-CP Towards Display and Development of Capripox Viral Like Particles Based on Immunogenic P32 Envelop Protein is the Homologous of the Vaccinia-Viral H3L Gene: An Insilico Approach

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Abstract

Viral-like particles are assembled from capsid protein structural subunits of different viruses and have ability to establish research in biomedicals, like construction of novel safety vaccines, gene therapy vectors by delivering systems for nucleic acids, small biomolecules and diagnostics. Papaya Mosaic Viral nanoparticals can provide as a vaccine candidate helps to increase the immunity by fusing the epitope based peptide antigen. Capripox viruses are the genus comprises Lymphy skin-disease, Sheep and Goat pox Viruses are notified by The World Animal Health Organization (OIE) based on their economic impotence act as a transboundary animal diseases viruses of sheep, goat, and cattle's respectively. Plant viral based innovative vaccines have been emerged ineffective vaccine development. This research describes the engineering and development of a new vaccine candidate by display immunogenic peptide using the carrier capsid protein of Papaya Mosaic Virus. The Capripox virus P32 immunogenic protein is homologous of the vaccinia virus H3L gene displayed PapMV CP. The antigenicity of P32 protein epitope lowest score among epitopes C-terminally docked epitopes are EP6 > EP3 > EP8 as well the lowest score among epitopes N-terminally docked epitopes are EP8 > EP3 > EP6 presented on the N-terminus of PMV CP region which are found to be suitable for epitope display. And these modelled immunogenic peptide could be used to develop a viral like particles. Epitope based Antibody developed against immunogenic epitopic regions can contribute to a novel and robust protection from infection. As well might be used for developing cost effective detection kits for Transboundary animal disease viruses.

Keywords Viral-like particles · Capripox viruses · Papaya mosaic viral capsid protein · B-Cell epitopes

Abbreviations

VLPS	Viral-like particles
PMV CP	Papaya mosaic virus capsid protein
LSDV	Lymphy skin-disease virus
SPPV	Sheeppox virus
GPPV	Goatpox virus
EPs	Epitopes

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Introduction

Virus-like particles have a multiple epitopes display on the surface comprises from viral antigens and have an ability self-assembled arranges the indigenous construction of viruses and they are lack of their viral genomes. These viral-like particles can be formed from nucleocapsid or envelope proteins alone (Pushko et al. 2013). Based on high advantages of viral-like particles in safety, manufacturing and immunogenicity emerged as a foremost vaccine platform (Chen and Lai 2013). In biomedical applications of viral like particles shown more effective and safety a novel subunit

vaccine, gene therapy vectors and diagnostic kits constructions. Plant viruses are emerging as promising vectors for use in innovative vaccination and development of diagnostic kits. Formation and production of viral like particles of immunogenic recombinant proteins in numerous plant systems have been deeply investigated and improved. In Vaccinology plant derived microbicides, vaccines and antibodies shown great attention and implemented. For the development of safety and effective mucosal and orally delivered plant created or produced viral like particles need a nominal process of the plant tissue (Santi et al. 2006). To develop a viral like particles and viral-based vectors, Papaya Mosaic Virus based viral nanoparticles are the competent vaccine platform. The immunogenic protein like epitopes or peptide antigens are fused with the capsid protein of mosaic virus at N-terminal side and C-terminal side of resulting in nanoparticles presenting surface-displays the epitopes. The fusion between immunogenic peptides and coat protein shows the stabilize the epitope towards carrying and enhances immunogenicity (Babin et al. 2013).

In the Poxviridae family, Capripoxvirus are large dsDNA, and enveloped viruses characterized by clinical symptoms like fever, papules, vesicles (rarely), internal lesions and death. These diseases are economically important and most serious infectious viral diseases of animal poxviruses which cause diseases in cattle, goat, and sheep and by a lumpy skin disease viral infection (LSDV), Goatpox virus (GPPV) and sheeppox virus (SHPPV) (Bhanuprakash et al. 2006; Tarello and Kinne 2007; Mirzaie et al. 2015). These Capripoxviruses based on their infectious and economic importance listed in group A diseases in the Office International disease Epizooties (OIE) (Varshovi et al. 2017). Capripoxviruses have the threats to become potential emerging disease because of global climatic change and due to porous international boundaries which facilitate for immigration of animals and their animal products from neighboring countries. These diseases are endemic in Africa, Middle East, Europe and Asia. The disease is transmitted through the infected animal direct contact or by contaminated objects (Tuppurainen et al. 2015). In cattle's LSD viral infection is a serious significant Transboundary, emerging skin viral disease and it is recognized and included in the OIE list (Mhemid and Hassan 2015). The capripox viral (sheep and goat pox virus) immunogenic p32 envelop protein is the homologous of P35 encoded by vaccinia viral H3L gene and locate membrane surface of the viral particles (Zhou et al. 2012).

Plant viruses are acting as emerging vectors to use and develop a novel vaccination strategies (Nuzzaci et al. 2006). VLC based Vaccines Engerix® and Recombivax® for hepatitis B and Gardasil® and Cervarix® for human papillomavirus commercially licensed (Crisci et al. 2013). Available vaccines against capripox viruses shows cross-protection and failure to provoke long-term protection against the various serovars of the pathogenic Capripox virus mixed strains.

The main aim is to predicit and map the B-cell epitopes (BCEp) on P32 in order to find a novel epitope based vaccine candidate. Expression of capsid proteins in microbial systems and their assembly into VLPs facilitate mass production of CP in vitro (Rostami et al. 2014). Therefore, the intend of this work was to modele and display of possible antigenic P32 BCEp on the surface of PapMV CP.

Materials and Methods

Retrieval of Sequence and Multiple Sequence Alignments

Capripox virus—P32 envelop protein is the homolog of P35 protein encoded H3L gene of vaccinia virus. The amino acid sequences was accessed from UniProtKB and National Centre for Biotechnology Information center (NCBI) (www.ncbi.nlm.nih.gov). As well Papaya Mosaic Virus Coat Protein (PMV CP) was also downloaded to predict the tertiary structure. The UniProt ID for Coat Protein on Papaya Mosaic Virus was P16596; and the immunogenic p32 accession numbers are AYI57795.1 is the major envelope protein Sheeppox virus, AAQ88213.1 envelope protein of Goat pox virus and AAD31773.1 P32 antigen of LSDV from these three Capripox viral p32 immunogenic protein carried out the NCBI protein BLAST (Altschul et al. 1997, 2005) multiple sequence alignment to understand structural similarity. As well, we carried out MSA of different sheep pox viral immunogenic p32 protein. The sequence numbers are AHB72723, AHB72720, AHI18587, ACR20671, AYO90717, AYO90726, AYO90724, AYO90723, AYO90722, AYO90721, AYI57795. The physico-chemical characterization of Capripox viral major envelop protein and papaya mosaic viral coat proteins was carried out by using Expasy's ProtParam server (https://us.expasy.org/tools/protparam.html).

Homology Modeling and Structural Validation

Homology modelling and 3D structural prediction of PMV CP and Capripox vial envelop p32 proteins was carried out by using phyre2, (https://www.sbg.bio.ic.ac.uk/phyre2) (Kelley et al. 2015) and shows the advanced remote homology recognition method to construct 3D models. The evaluation of protein structural models was carriedout by using PROCHECK, Swiss-PdbViewer software and finally chosen model were 3D visualization was done using PyMOL (Guex and Peitsch 1997).

In Silico Epitope Mapping

The main aim epitope prediction and mapping to identify and predict the binding sites of antigen–antibody interactions to enhance immuneresponce as well improvement of effective diagnostics, vaccines and immunotherapeutic compounds. The sequential, conformational immunogenic epitope of Capripox viral p32 were mapped from its predicted model using IEDB ElliPro: Antibody Epitope Prediction server (https://tools.immuneepitope.org/). The predicted epitopes were further analyzed prapable antigen or non-antigen by VaxiJen server with criteria of 0.3 threshold values and virus as the target organism. Based on the principle an ACC (Auto cross covariance) predicts defensive antigens renovation of protein sequence into identical vectors of principle amino acid. The predicted and selected epitope were modelled by PEP-FOLD server.3 (Idris et al. 2018).

Coat Protein-Epitope Docking

The HADDOCK is a high ambiguous interaction restraints online server used for the prediction of protein–protein flexible docking approach to model a biomolecular complexes. Based on highest low intermolecular energy cluster and representative docked structures was chosen analyzed for inter-molecular interactions. P32 epitopes were docked at the C and N terminal of the PMV CP using HADDOCK 2.2 webserver. (https://milou.science.uu.nl/services/HADDOCK2.2/haddock.php) (Ikram et al. 2018; Bhavaniprasad et al. 2013). The active and passive residues- required for protein docking studies- in PMV CP and P32 were predicted by, SPPIDER which were integrated in a single platform by CPORT. The epitopes were docked at the N and C terminal of PMV CP, with the corresponding active residues chosen at the instance. The PMV CP-Epitope docked complex with the lowest docked score was chosen at each termini for further analysis (Porollo and Meller 2007). Moming was Mapped B-cell epitopes and expressed N-terminal region and C-terminal region of NP of hemorrhagic fever virus (Moming et al. 2018) to understanding the structure and functions efficiently towards multi-epitope detection antigen as well epitope based vaccine.

Results

Physicochemical Properties and Multiple Sequence Alignments

The physicochemical structural properties of three envelop p32 proteins of capripox virus and PapMV coat protein was done. The parameters included the pI values, amino acid composition, coefficient, atomic composition, molecular weight aliphatic index, instability index and hydropathicity the detailed results were showed in Table 1.

The BLAST Results of capripoxvirus p32 envelop proteins were shown identies of Lumpy skin disease virus_AAD31773.1 P32 antigen shown 315/323(98%) Identities, Goatpox virus_AAQ88213.1 envelope protein P32 310/323(96%) identies with sheeppox virus Sheeppox virus_AYI57795.1

Multiple sequence alignment of major envelop p32 protein selected sequences were shown variation at 26 position GPV virus Glycine (G) is present instead of Aspartic (D) acid where as in LSDV and SPV shown Aspartic acid. 46 amino acid position Asparagine (N) is similar both LSDV and SPV, SPV envelop protein shown extra Aspartic acid at 54 position where as in LSDV and GPV shown a gap or absent aminoacid at particular position. LSDV and GPV shown similar amino acid at 132, 134 positions where as in

Table 1 Parameters computed using Expasy's ProtParam tool

Property	Values of P32 major envelope protein			PMV CP
	Sheeppox virus	Goatpox virus	Lumpy skin disease virus	
Number of amino acides	323	322	322	215
Molecular weight	37583.58	37474.57	37593.62	23033.09
Theoretical pl	8.24	8.84	8.24	7.73
Total number of negatively charged residues(Asp+Glu)	38	36	38	15
Total number of positively residues (Arg+Lys)	40	41	40	16
Extinction coefficient (1.330, assuming all pairs of Cys residues form cystines)	49975	51465	49975	17085
Extinction coefficient* (1.326, assuming all Cys residues are reduced)	49850	51340	49850	16960
Instability index	28.63	26.49	28.18	46.37
Aliphatic index	103.81	100.78	102.61	72.28
Grand average of hdropathicity	− 0.041	− 0.042	− 0.03	− 0.148

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                                        Epi-6      Epi-1
AHI18587/Jilin/MEP                      MADIPLYVIPIVGREISDVVPELKSDNDIFYKKVDTVKDFKNSDVNFFLKDKKDDISLSY   60
AHB72720/GanSuGT/11/2012/China          MADIPLYVIPIVGREISDVVPELKSDNDIFYKKVDTVKDFKNSDVNFFLKDKKDDISLSY   60
AYI57795/NIVEDI/Jamakandi/2017          MADIPLYVIPIVGREISDVVPELKSDNDIFYKKVDTVKDFKNSDVNFFLKDKKDDISLSY   60
AY090717/36/16/Tunis                    MADIPLYVIPIVGREISDVVPELKSDNDIFYKKVDTVKDFKNSDVNFFLKDKKDDISLSY   60
AY090726/1517/12F/Tunisia               MADIPLYVIPIVGREISDVVPELKSDNDIFYKKVDTVKDFKNSDVNFFLKDKKDDISLSY   60
AY090724/3337/10                        MADIPLYVIPIVGREISDVVPELKSDNDIFYKKVDTVKDFKNSDVNFFLKDKKDDISLSY   60
AY090723/TN                             MADIPLYVIPIVGREISDVVPELKSDNDIFYKKVDTVKDFKNSDVNFFLKDKKDDISLSY   60
AY090722/TN                             MADIPLYVIPIVGREISDVVPELKSDNDIFYKKVDTVKDFKNSDVNFFLKDKKDDISLSY   60
AY090721/TN09/16                        MADIPLYVIPIVGREISDVVPELKSDNDIFYKKVDTVKDFKNSDVNFFLKDKKDDISLSY   60
ACR20671/Pune/08                        MADIPLYVIPIVGREISDVVPELKSDNDIFYKKVDTVKDFKNSDVNFFLKDKKDDISLSY   60
AHB72723/GanSuHN/12/2012/China          MADIPLYVIPIVGREISDVVPELKSDNDIFYKKVDTVKDFKNSDVNFFLKDKKDDISLSY   60
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                                             Epi-2                             Epi-3
AHI18587/Jilin/MEP                      KLLIWEKVEKSGGVENFTEYFSGLCNALCTKEAKSSIAKHFSLWKSYADADIKNSENKFI   120
AHB72720/GanSuGT/11/2012/China          KLLIWEKVEKSGGVENFTEYFSGLCNALCTKEAKSSIAKHFSLWKSYADADIKNSENKFI   120
AYI57795/NIVEDI/Jamakandi/2017          KLLIWEKVEKSGGVENFTEYFSGLCNALCTKEAKSSIAKHFSLWKSYADADIKNSENKFI   120
AY090717/36/16/Tunis                    KLLIWEKVEKSGGVENFTEYFSGLCNALCTKEAKSSIAKHFSLWKSYADADIKNSENKFI   120
AY090726/1517/12F/Tunisia               KLLIWEKVEKSGGVENFTEYFSGLCNALCTKEAKSSIAKHFSLWKSYADADIKNSENKFI   120
AY090724/3337/10                        KLLIWEKVEKSGGVENFTEYFSGLCNALCTKEAKSSIAKHFSLWKSYADADIKNSENKFI   120
AY090723/TN                             KLLIWEKVEKSGGVENFTEYFSGLCNALCTKEAKSSIAKHFSLWKSYADADIKNSENKFI   120
AY090722/TN                             KLLIWEKVEKSGGVENFTEYFSGLCNALCTKEAKSSIAKHFSLWKSYADADIKNSENKFI   120
AY090721/TN09/16                        KLLIWEKVEKSGGVENFTEYFSGLCNALCTKEAKSSIAKHFSLWKSYADADIKNSENKFI   120
ACR20671/Pune/08                        KLLIWEKVEKSGGVENFTEYFSGLCNALCTKEAKSSIAKHFSLWKSYADADIKNSENKFI   120
AHB72723/GanSuHN/12/2012/China          KLLIWEKVEKSGGVENFTEYFSGLCNALCTKEAKSSIAKHFSLWKSYADADIKNSENKFI   120
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                                                           Epi-8           Epi-4
AHI18587/Jilin/MEP                      VVIEDDNTLKDSVIIHNIMIEMQEKNIDIFQLRETFHNSNSRILFNQENNNFMYSYTGGY   180
AHB72720/GanSuGT/11/2012/China          VVIEDDNTLKDSIIIHNIIIEMQEKNIDIFQLRETFHNSNSRILFNQENNNFMYSYTGGY   180
AYI57795/NIVEDI/Jamakandi/2017          VVIEDDNTLKDSIIIHNIIIEMQEKNIDIFQLRETFHNSNSRILFNQENNNFMYSYTGGY   180
AY090717/36/16/Tunis                    VVIEDDNTLKDSIIIHNIIIEMQEKNIDIFQLRETFHNSNSRILFNQENNNFMYSYTGGY   180
AY090726/1517/12F/Tunisia               VVIEDDNTLKDSIIIHNIIIEMQEKNIDIFQLRETFHNSNSRILFNQENNNFMYSYTGGY   180
AY090724/3337/10                        VVIEDDNTLKDSIIIHNIIIEMQEKNIDIFQLRETFHNSNSRILFNQENNNFMYSYTGGY   180
AY090723/TN                             VVIEDDNTLKDSIIIHNIIIEMQEKNIDIFQLRETFHNSNSRILFNQENNNFMYSYTGGY   180
AY090722/TN                             VVIEDDNTLKDSIIIHNIIIEMQEKNIDIFQLRETFHNSNSRILFNQENNNFMYSYTGGY   180
AY090721/TN09/16                        VVIEDDNTLKDSIIIHNIIIEMQEKNIDIFQLRETFHNSNSRILFNQENNNFMYSYTGGY   180
ACR20671/Pune/08                        VVIEDDNTLKDSIIIHNIIIEMQEKNIDIFQLRETFHNSNSRILFNQENNNFMYSYTGGY   180
AHB72723/GanSuHN/12/2012/China          VVIEDDNTLKDSIIIHNIIIEMQEKNIDIFQLRETFHNSNSRILFNQENNNFMYSYTGGY   180
                                        ************.***** *****************************************

                                                          Epi-7               Epi-5
AHI18587/Jilin/MEP                      DFTLSAYVIRLSSAIKIINEIIKNKGISTSLSFEMYKLEKELKLNRQVLNDSSKYILHNT   240
AHB72720/GanSuGT/11/2012/China          DFTLSAYVIRLSSAIKIINEIIKNKGISTSLSFEMYKLEKELKLNRQVLNDSSKYILHNT   240
AYI57795/NIVEDI/Jamakandi/2017          DFTLSAYVIRLSSAIKIINEIIKNKGISTSLSFEMYKLEKELKLNRQVLNDSSKYILHNT   240
AY090717/36/16/Tunis                    DFTLSAYVIRLSSAIKIINEIIKNKGISTSLSFEMYKLEKELKLNRQVLNDSSKYILHNT   240
AY090726/1517/12F/Tunisia               DFTLSAYVIRLSSAIKIINEIIKNKGISTSLSFEMYKLEKELKLNRQVLNDSSKYILHNT   240
AY090724/3337/10                        DFTLSAYVIRLSSAIKIINEIIKNKGISTSLSFEMYKLEKELKLNRQVLNDSSKYILHNT   240
AY090723/TN                             DFTLSAYVIRLSSAIKIINEIIKNKGISTSLSFEMYKLEKELKLNRQVLNDSSKYILHNT   240
AY090722/TN                             DFTLSAYVIRLSSAIKIINEIIKNKGISTSLSFEMYKLEKELKLNRQVLNDSSKYILHNT   240
AY090721/TN09/16                        DFTLSAYVIRLSSAIKIINEIIKNKGISTSLSFEMYKLEKELKLNRQVLNDSSKYILHNT   240
ACR20671/Pune/08                        DFTLSAYVIRLSSAIKIINEIIKNKGISTSLSFEMYKLEKELKLNRQVLNDSSKYILHNT   240
AHB72723/GanSuHN/12/2012/China          DFTLSAYVIRLSSAIKIINEIIKNKGISTSLSFEMYKLEKELKLNRQVLNDSSKYILHNT   240
                                        ************************************************************

AHI18587/Jilin/MEP                      KYLSKKRANEMKNGIWNRVGKWMAHRFPDFSYYVSHPLVSFFGIFDISIIGALIILFIII   300
AHB72720/GanSuGT/11/2012/China          KYLSKKRANEMKNGIWNRVGKWMAHRFPDFSYYVSHPLVSFFGIFGISIIGALIILFIII   300
AYI57795/NIVEDI/Jamakandi/2017          KYLSKKRANEMKNGIWNRVGKWMAHRFPDFSYYVSHPLVSFFGIFDISIIGALIILFIII   300
AY090717/36/16/Tunis                    KYLSKKRANEMKNGIWNRVGKWMAHRFPDFSYYVSHPLVSFFGIFDISIIGALIILFIII   300
AY090726/1517/12F/Tunisia               KYLSKKRANEMKNGIWNRVGKWMAHRFPDFSYYVSHPLVSFFGIFDISIIGALIILFIII   300
AY090724/3337/10                        KYLSKKRANEMKNGIWNRVGKWMAHRFPDFSYYVSHPLVSFFGIFDISIIGALIILFIII   300
AY090723/TN                             KYLSKKRANEMKNGIWNRVGKWMAHRFPDFSYYVSHPLVSFFGIFDISIIGALIILFIII   300
AY090722/TN                             KYLSKKRANEMKNGIWNRVGKWMAHRFPDFSYYVSHPLVSFFGIFDISIIGALIILFIII   300
AY090721/TN09/16                        KYLSKKRANEMKNGIWNRVGKWMAHRFPDFSYYVSHPLVSFFGIFDISIIGALIILFIII   300
ACR20671/Pune/08                        KYLSKKRANEMKNGIWNRVGKWMAHRFPDFSYYVSHPLVSFFGIFDISIIGALIILFIII   300
AHB72723/GanSuHN/12/2012/China          KYLSKKRANEMKNGIWNRVGKWMAHRFPDFSYYVSHPLVSFFGIFDISIIGALIILFIII   300
                                        *********************************************.**************

AHI18587/Jilin/MEP                      MIIFNLNSKLLWFLAGMLFTYII      323
AHB72720/GanSuGT/11/2012/China          MIIFNLNSKLLWFLAGMLFTYIV      323
AYI57795/NIVEDI/Jamakandi/2017          MIIFNLNSKLLWFLAGMLFTYII      323
AY090717/36/16/Tunis                    MIIFNLNSKLLWFLAGMLFTYII      323
AY090726/1517/12F/Tunisia               MIIFNLNSKLLWFLAGMLFTYII      323
AY090724/3337/10                        MIIFNLNSKLLWFLAGMLFTYII      323
AY090723/TN                             MIIFNLNSKLLWFLAGMLFTYII      323
AY090722/TN                             MIIFNLNSKLLWFLAGMLFTYII      323
AY090721/TN09/16                        MIIFNLNSKLLWFLAGMLFTYII      323
ACR20671/Pune/08                        MIIFNLNSKLLWFLAGMLFTYII      323
AHB72723/GanSuHN/12/2012/China          MIIFNLNSKLLWFLAGMLFTYIV      323
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◂**Fig. 1** Multiple sequence alignment of P32: Multiple sequence alignment of P32 from 11 different strains of Capripox viruses were tested by T-Coffee program (https://tcoffee.crg.cat/apps/tcoffee/do:regular). Among all selected capripox viral p32 sequences colured regions in the above alignment shown perfect sequence alignment. And the predicted epitopes were marked as boxes in the particular regions

SPV at 132 positions Serine and 134 position Isoleucine variations was observed. at 290, 325 amino acid position SPV and LSDV were shown Isoleucine but GPV shown Methionine at 290 position and at 322 position Valine variation. SPV and GPV were shown similar amino acid at 305 position where as LSDV Aspartic acid (D) was observed. multiple sequence alignment of different sheeppox viral immunogenic p32 protein and their epitope predicted sequences were showened in Fig. 1.These results may help to analyse identification species basic envelop based diagnostic marker development.

Homology Modelling and Structural Validation

The immunogenic p32 protein of and papaya mosaic virus tertiary structure was predicted by PHYRE2, this server can perform ab initio modelling to improve models figure. The modelled structure was validated by Ramachandran plot generated using Procheck and RAMPAGE software (Lovell et al. 2002). The detailed protein structural prediction 3D modelled and validation of proteins results were shown below images. PMV CP predicted and modelled protein showed in Fig. 2 and P32 protein showed in Fig. 3.

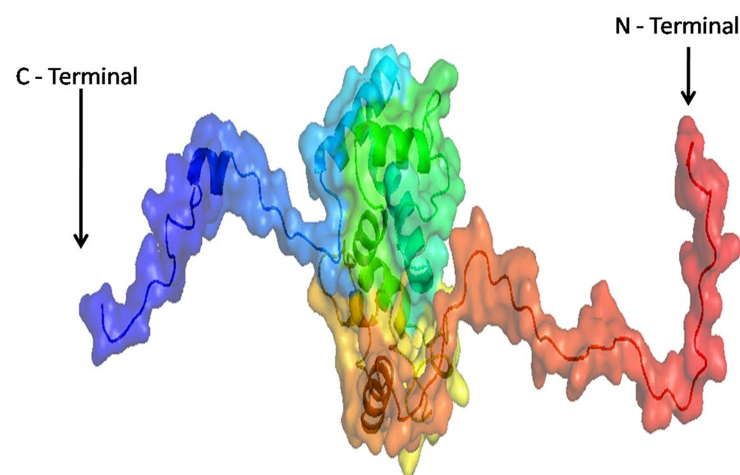
In Silico Epitope Mapping and Probable Antigen Validation

The predicted epitope peptides length of P32 is these positions—EP1 (21–36), EP2 (66–94), EP3 (110–118), EP4 (155–181), EP5 (220–224), EP6 (11–19), EP7 (199–210), EP8 (140–147) (Fig. 2). Further analysis of these epitopes were verified on VaxiJen web server, where the antigenicity values were; EP1 (0.1976), EP2 (0.3483), EP3 (0.5925), EP4 (0.3671), EP5 (−), EP6 (0.7832), EP7 (0.2495) and EP8 (1.5581). All probable antigenic epitopes (EP3, EP6 and EP8) was taken for further analysis. The results were tabulated in Table 2.

Coat Protein-Epitope Docking

Selected probable antigenic epitopes (EP3, EP6 and EP8) were used to display on Papaya Mosaic Virus Coat protein. HADDOCK web server clustered the structures and the top ten were analyzed as they have the most reliable structural interaction based on the score obtained by each cluster. The epitopes when individually docked at N and C-terminal region of the PMVCP (Kumar et al. 2015). The docked

(a) Structural model of PaMV CP protein.



(b) Ramachandran plot PaMV CP

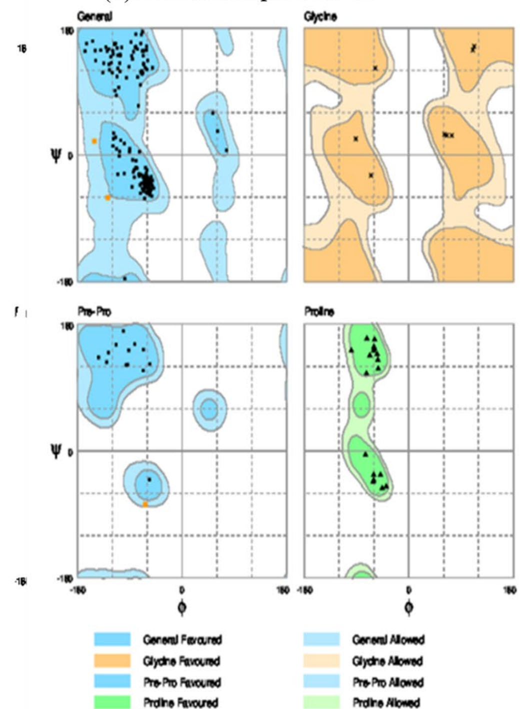


Fig. 2 Modelled and validated Papaya Mosaic Viral Coat Protein Pyre2 and RAMPAGE

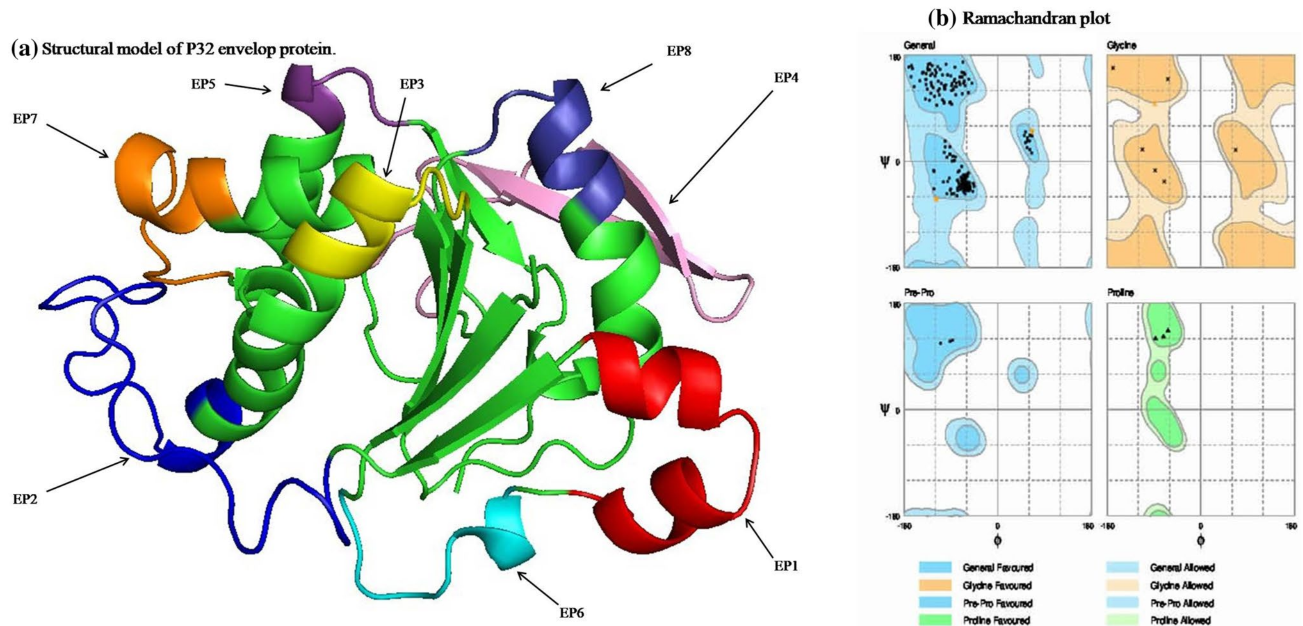


Fig. 3 Modelled and predicted structure of p32 protein and predicted different epitopic regions highlighted in different colours

Table 2 Prediction and verification of P32 epitopes by VaxiJen antigen prediction server

Epitope Sl. No	Start	End	Peptide	Number of residues	Score	VaxiJen probable antigenic score
Ep1	21	36	PELKSDNDIFYKKVDT	16	0.789	0.1976 (NP)
Ep2	66	94	EKVEKSGGVENFTEYFSGLCNALCTKEAK	29	0.711	0.3483 (NP)
Ep3	110	118	ADIKNSENK	9	0.688	0.5925 (AP)
Ep4	155	181	TFHNSNSRILFNQENNNFMYSYTGGYD	27	0.673	0.3671 (NP)
Ep5	220	224	KELKL	5	0.643	–
Ep6	11	19	IVGREISDV	9	0.613	0.7832 (AP)
Ep7	199	210	NEIIKNKGISTS	12	0.614	0.2495 (NP)
Ep8	140	147	IEMQEKNI	8	0.526	1.5581 (AP)

A probable antigen, *NA* probable non-antigen, *NP* non probable antigen, *AP* probable antigen

results given scores based on Van der Waal's energy, electrostatic energy, desolvation energy, binding energy and buried surface area. Docking results were analyzed and tabulated in detail Table 3 (Dominguez et al. 2003; van Zundert et al. 2016).

EP6 had the lowest score among other epitopes terminally docked. At the C terminal of PMV CP, the score was -62.0 ± 5.2 and at the N terminal it was -55.4 ± 2.0. The lowest score among epitopes C-terminally docked is EP6 > EP3 > EP8 as well the lowest score among epitopes N-terminally docked is EP8 > EP3 > EP6 and the models are displayed in surface models using PyMOL showed in Fig. 4 and the Interaction between PMV CP at C and N-terminus regions with CEp3, CEp6 and CEp8 Epitopes was analysed by PDB SUM (Laskowski et al. 2018) showed in Figs. 5 and 6. Evaluation of predicted models by Rampage the results were tabulated in Table 4.

Interaction Between PMV CP N and C-Terminus Regions with Epitopes

CEp3

The interaction between the PaMV CP with epitope 3at C-terminus was observed the number of hydrogen bonds 7 and number of non-bonded contacts 66. C-terminus protein interactive active amino acid residues LYS 198, GLN 200, SER 202, SER 204, SER 204, PRO 206, GLU 215 interacted

Table 3 Predicted and assessment of docked complexes

Models of PMV CP-epitope		HADDOCK score	Z-score	Van der Waals energy (Kcal mol^{-1})	Electrostatic energy (Kcal mol^{-1})	Desolvation energy (Kcal mol^{-1})	Restraints violation energy (Kcal mol^{-1})	Buried surface area
Coat protein terminal	Epitope name							
Carboxy terminal (C)	EP3	− 55.6 ± 8.2	− 1.7	− 29.6 ± 1.9	− 135.0 ± 49.1	− 8.4 ± 4.0	94.2 ± 29.61	954.8 ± 38.8
	EP6	− 62.0 ± 5.2	− 1.4	− 33.3 ± 4.5	− 75.5 ± 26.4	− 21.7 ± 1.6	81.8 ± 42.08	976.1 ± 43.6
	EP8	− 52.4 ± 2.4	− 1.4	− 24.9 ± 8.9	− 117.8 ± 25.4	− 13.7 ± 3.3	97.5 ± 31.10	909.0 ± 72.0
Amino terminal (N)	EP3	− 56.7 ± 4.8	− 1.8	− 32.9 ± 4.3	− 102.7 ± 30.7	− 13.2 ± 9.6	98.5 ± 47.72	953.1 ± 84.4
	EP6	− 55.4 ± 2.0	− 1.6	− 34.5 ± 5.7	− 99.4 ± 35.7	− 8.3 ± 2.6	72.9 ± 35.11	1027.6 ± 78.3
	EP8	− 57.5 ± 2.1	− 1.9	− 35.5 ± 1.3	− 144.1 ± 12.9	− 6.6 ± 4.2	135.0 ± 34.00	1024.5 ± 61.6

with epitope 3 chain residues SER 6, ILE 3, LYS 4, LYS 4, LYS 4, ASN 8, LYS 9.

CEp6

The interaction between the PaMV CP with epitope 6 at C-terminus was observed the number of hydrogen bonds 8 and number of non-bonded contacts 73. C-terminus protein interactive active amino acid residues LYS 198, GLY 199, GLN 200, ILE 201, SER 204, PRO 206, THR 207, GLU 215 interacted with epitope 6 chain residues SER 6, ILE 3, LYS 4, LYS 4, LYS 4, ASN 8, LYS 9.

CEp8

The interaction between the PaMV CP with epitope 8 at C-terminus was observed the number of hydrogen bonds 8

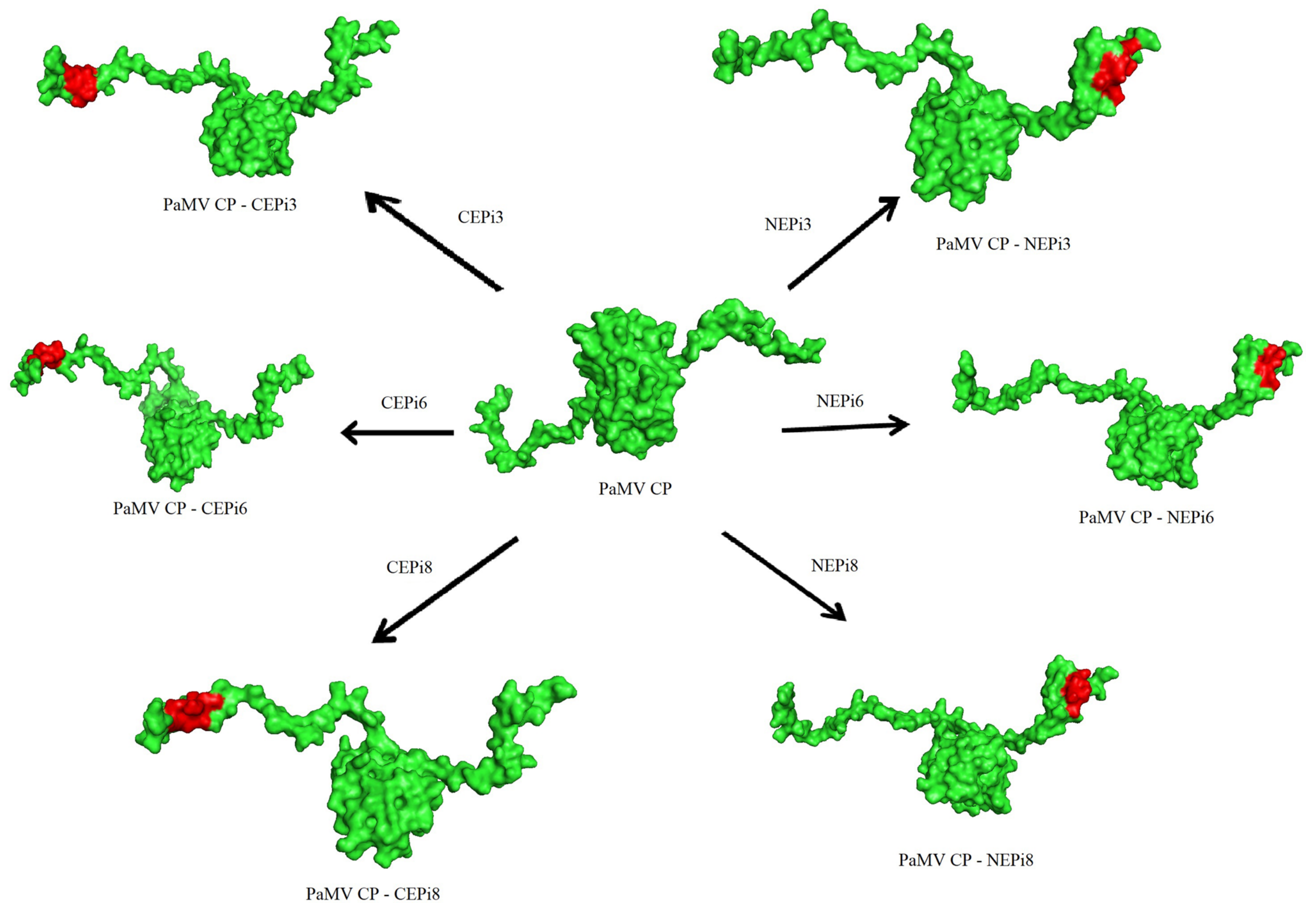


Fig. 4 PMV CP- immunogenic Capripox viral envelop P32 protein epitopes docking at N, C termini: Protein–epitope docking of P32 epitopes at N, C by using HADDOCK server and the models are displayed in surface models using PyMOL

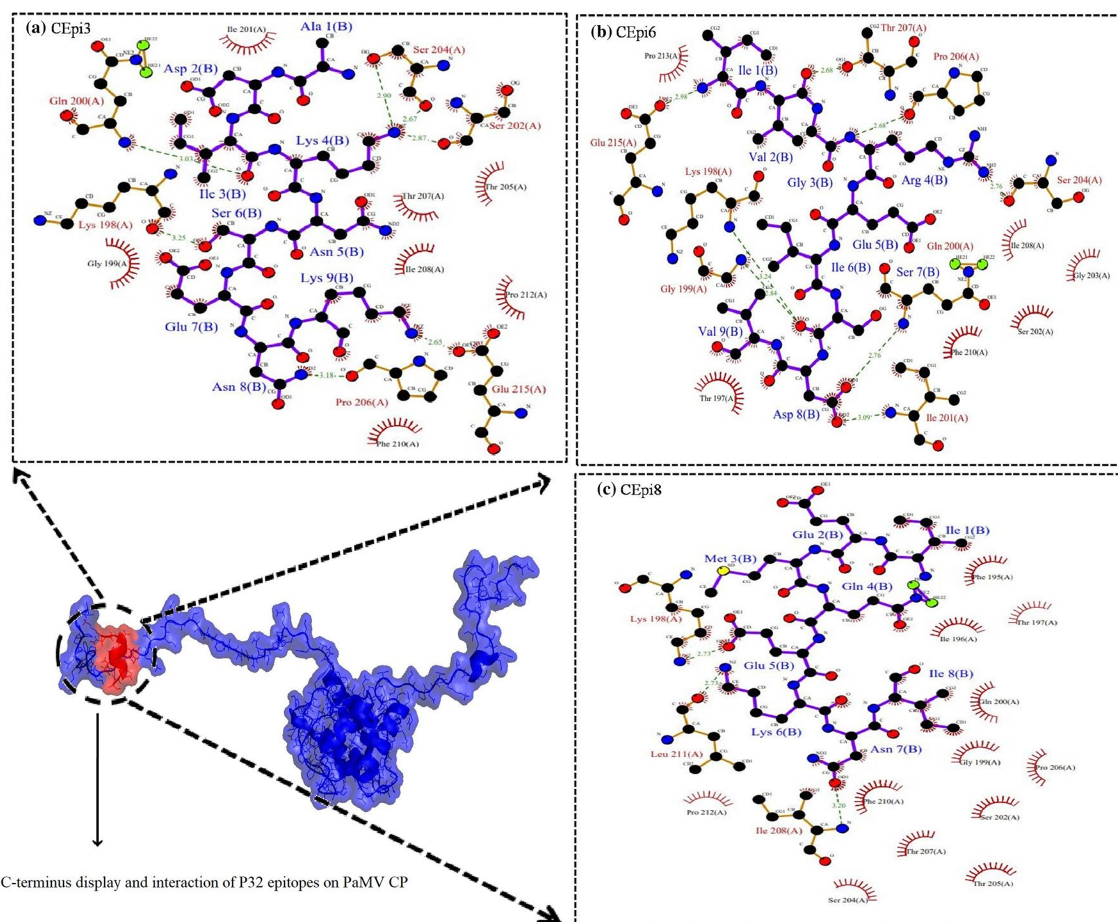


Fig. 5 Interaction between PMV CP at C-terminus regions with CEp3, CEp6 and CEp8 epitopes

and number of non-bonded contacts 62. C-terminus protein interactive active amino acid residues LYS 198, ILE 208, LEU 211interacted with epitope 8 chain residues GLU 5, ASN 7, LYS 6.

NEp3

The interaction between the PaMV CP with epitope 3 at N-terminus was observed the number of hydrogen bonds 8 and number of non-bonded contacts 95. N-terminus protein interactive active amino acid residues LYS 3, THR 8, THR 8, ASN 10, ASN 10, ILE 16, ILE 16, GLN 18 interacted with epitope 3 chain residues LYS 9, ASP 2, ASN 5, SER 6, ASN 8, ASP 2, ILE 3, LYS 4.

NEp6

The interaction between the PaMV CP with epitope 6 at N-terminus was observed the number of hydrogen bonds 4 and number of non-bonded contacts 84. N-terminus protein interactive active amino acid residues MET 6, PRO 9, ALA 12, GLN 18 interacted with epitope 6 chain residues GLY 3, ARG 4, ARG 4, ASP 8.

NEp8

The interaction between the PaMV CP with epitope 8 at N-terminus was observed the number of hydrogen bonds 8 and number of non-bonded contacts 99. N-terminus protein interactive active amino acid residues SER 5, SER 7, ALA 15, ILE 16, GLN 18, GLN 18, GLU 19, MET 21 interacted with epitope 8 chain residues GLN 4, GLU 5, GLU 2, ILE 1 (Tables 5 and 6).

Discussion

Capripoxviruses are the genus comprises sheeppox, goatpox and Lymphyskin disease viruses in the poxviridae family, based on economic importance and infectious

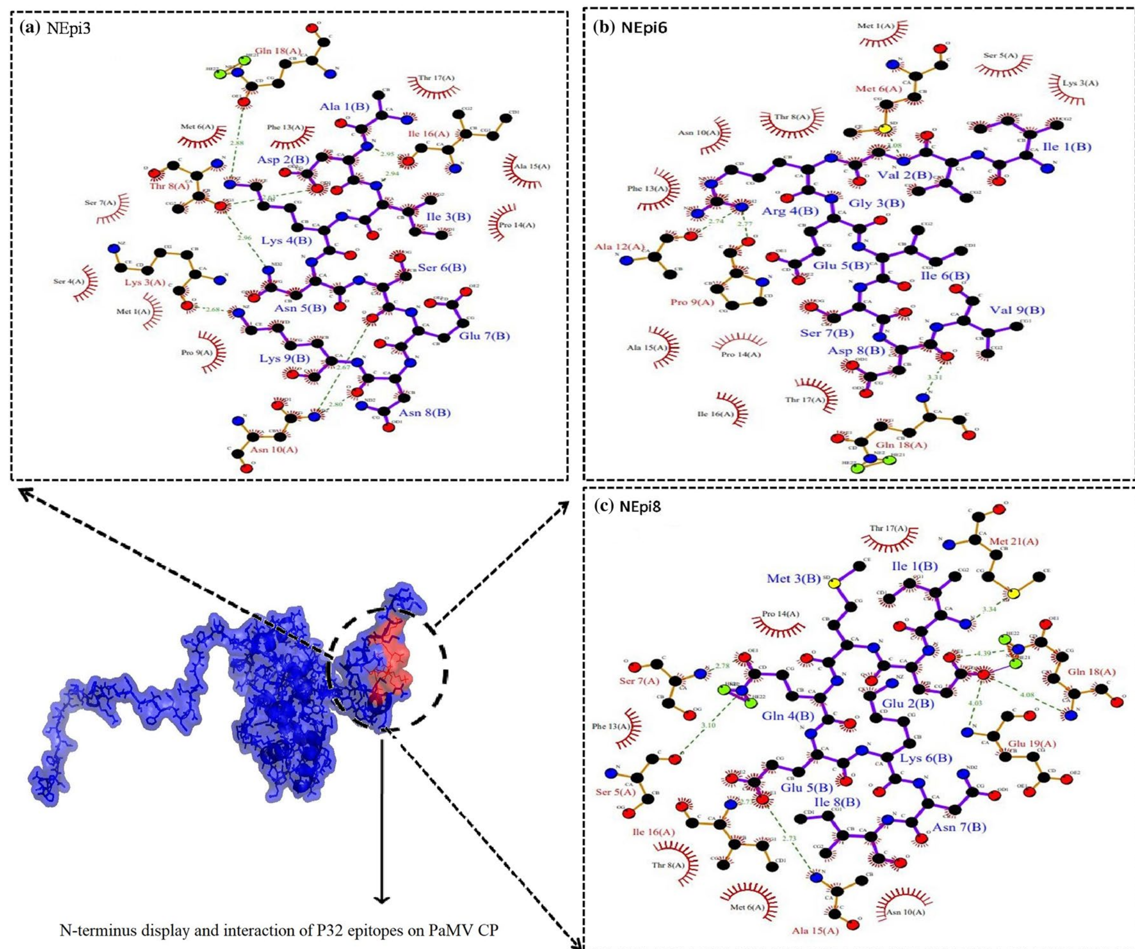


Fig. 6 Interaction between PMV CP at N-terminus regions with NEp3, NEp6 and NEp8 epitopes

Table 4 Evaluation of predicted models by Rampage

Models of PMV CP-epitope		Number of residues in favoured region	Number of residues in allowed region	Number of residues in outlier region
Coat protein terminal	Epitope name			
P32	–	210 (98.6%)	3 (1.4%)	0 (0.0%)
PMV	–	210 (98.6%)	3 (1.4%)	0 (0.0%)
Carboxy terminal (C)	EP3	204 (92.7%)	14 (6.4%)	2 (0.9%)
	EP6	203 (92.3%)	14 (6.4%)	3 (1.4%)
	EP8	206 (94.1%)	11 (5.0%)	2 (0.9%)
Amino terminal (N)	EP3	209 (95.0%)	10 (4.5%)	1 (0.5%)
	EP6	198 (90.0%)	20 (9.1%)	2 (0.9%)
	EP8	208 (95.0%)	10 (4.6%)	1 (0.5%)

nature these viruses are considered as the transboundary and OIE notifiable diseases of the developing the world and is always the threat of spreading of Capripox viruses into new geographic regions. The diseases show economic impact directly by causing morbidity and mortality as well by reducing reproduction performance, quality of wool and meat poisoning on international trade. Hence there is a need to identify Capripox virus isolates effects for both sheep and goats, leads may be able to develop single

Table 5 Interaction between PMV CP at C-terminus regions with CEp3, CEp6 and CEp8 epitopes

Protein chain A T O M 1							Epitope chain A T O M 2					
CEp3	Atom no	Atom name	Res name	Res no	Chain		Atom no	Atom name	Res name	Res no	Chain	Distance
1	1830	O	LYS	198	A	<–	2028	OG	SER	6	B	3.25
2	1836	N	GLN	200	A	–>	1999	O	ILE	3	B	3.03
3	1864	O	SER	202	A	<–	2007	NZ	LYS	4	B	2.87
4	1877	O	SER	204	A	<–	2007	NZ	LYS	4	B	2.67
5	1874	OG	SER	204	A	<–	2007	NZ	LYS	4	B	2.9
6	1893	O	PRO	206	A	<–	2048	ND2	ASN	8	B	3.18
7	1972	OE1	GLU	215	A	<–	2060	NZ	LYS	9	B	2.65
CEp6	Atom no	Atom name	Res name	Res no	Chain		Atom no	Atom name	Res name	Res no	Chain	Distance
1	1818	N	LYS	198	A	–>	2041	O	SER	7	B	3.24
2	1831	N	GLY	199	A	–>	2041	O	SER	7	B	2.84
3	1836	N	GLN	200	A	–>	2047	OD1	ASP	8	B	2.76
4	1848	N	ILE	201	A	–>	2048	OD2	ASP	8	B	3.09
5	1877	O	SER	204	A	<–	2010	NH2	ARG	4	B	2.76
6	1893	O	PRO	206	A	<–	1998	N	ARG	4	B	2.68
7	1898	OG1	THR	207	A	–>	1992	O	VAL	2	B	2.68
8	1973	OE2	GLU	215	A	<–	1976	N	ILE	1	B	2.98
CEp8	Atom no	Atom name	Res name	Res no	Chain		Atom no	Atom name	Res name	Res no	Chain	Distance
1	1825	NZ	LYS	198	A	–>	2023	OE2	GLU	5	B	2.73
2	1903	N	ILE	208	A	–>	2044	OD1	ASN	7	B	3.2
3	1944	O	LEU	211	A	<–	2033	NZ	LYS	6	B	2.73

immune targeting single vaccine to protect the species (Burranboina et al. 2018; Madhavan et al. 2016).

In this research firstly we carried out conservancy of immunogenic envelop p32 protein between different species of SPPV, GPV and LSDV. As well-screened 11 sheeppox viral conservancy of p32 protein epitopes was carried out towards the study of universal epitopes based vaccine development requires conserved amino acids of a protein among the various pathogenic strains. Multiple amino acid sequence alignment of p32 for 11 different strains of sheeppox virus NIVEDI/Jamakandi/2017 (AYI57795), GanSuHN/12/2012/China (AHB72723), GanSuGT/11/2012/China (AHB72720), Jilin (AHI18587), 36/16 Tunis (AYO90717), 1517/12F Tunisia (AYO90726), 3337/10 (AYO90724), TN 13/15 (AYO90723), TN 10/16 (AYO90722), TN09/16 (AYO90721), Pune-08 (ACR20671), Were analyzed by using the T-Coffee program Fig. 1.

Viral like particles are the multiprotein structures mimicking viable native viruses, in immunogenic antigen structure but lack of the viral genomic material subsequently they are non-replicative with non-infectious nature as well they retain their capability to penetrate cells and shows the immense applications like they offer a safe substitute to inactivated and attenuated viral vaccine enhancement (Naskalska and Pyrc 2015). These VLPs are the appearance to the native form virus purified from infected source plants as well non-infectious. VLPs are being used by the polyvalent foreign epitope peptide display on their viral capsid protein surface to improve their presentation, immunogenicity as well host immune reaction (Kumar et al. 2009). Plant viral capsid proteins put forward the benefit of uniformity with respect to size, shape and have capability to self assembling into highly repeating nano- VLPs structures. Plant-based VLPS have a capable to exhibit tolerance to against pH and high temperature, structurally particular chemical attachment sites and resist intracellular environment like resist towards proteases and nucleases as well as these VLPs have a cargo capacity like they may suitable intended for transporting drugs to the affected area. Due to nonpathogenic nature of plant based viral nanoparticles may ideal selection for therapeutic applications. These structures are lack of viral genomic material, hence they are non-replicative or causing any type of infection (Shoeb and Hefferon 2019).

The immunogenic peptide display on a suitable platform based on evaluating the binding capability of epitope peptide-like display on surface of phage, bacteria, insect, yeast cells or mammalian cells (Potocnakova et al. 2016). Babin et al. 2013 was studied the fusion of the epitope stabilizes and it improves the immunogenicity. The PMV vaccine platform have a ability to provoke a enduring memory response

Table 6 Interaction between PMV CP at N – Terminus regions with NEp3, NEp6 and NEp8 Epitopes

Protein chain A T O M 1							Epitope chain A T O M 2					
NEp3	Atom no	Atom name	Res name	Res no	Chain		Atom no	Atom name	Res name	Res no	Chain	Distance
1	30	O	LYS	3	A	<–	2060	NZ	LYS	9	B	2.68
2	68	OG1	THR	8	A	–>	1987	OD1	ASP	2	B	2.63
3	68	OG1	THR	8	A	<–	2019	ND2	ASN	5	B	2.96
4	86	ND2	ASN	10	A	–>	2031	O	SER	6	B	2.67
5	86	ND2	ASN	10	A	–>	2052	O	ASN	8	B	2.8
6	139	O	ILE	16	A	<–	1982	N	ASP	2	B	2.95
7	139	O	ILE	16	A	<–	1991	N	ILE	3	B	2.94
8	155	OE1	GLN	18	A	<–	2007	NZ	LYS	4	B	2.88
NEp6	Atom no	Atom name	Res name	Res no	Chain		Atom no	Atom name	Res name	Res no	Chain	Distance
1	52	SD	MET	6	A	<–	1993	N	GLY	3	B	3.08
2	79	O	PRO	9	A	<–	2010	NH2	ARG	4	B	2.77
3	105	O	ALA	12	A	<–	2010	NH2	ARG	4	B	2.74
4	149	N	GLN	18	A	–>	2050	O	ASP	8	B	3.31
NEp8	Atom no	Atom name	Res name	Res no	Chain		Atom no	Atom name	Res name	Res no	Chain	Distance
1	46	O	SER	5	A	<–	2011	NE2	GLN	4	B	3.1
2	56	N	SER	7	A	–>	2010	OE1	GLN	4	B	2.78
3	125	N	ALA	15	A	–>	2022	OE1	GLU	5	B	2.73
4	131	N	ILE	16	A	–>	2022	OE1	GLU	5	B	2.73
5	149	N	GLN	18	A	–>	1992	OE2	GLU	2	B	2.88
6	156	NE2	GLN	18	A	–>	1991	OE1	GLU	2	B	2.77
7	161	N	GLU	19	A	–>	1992	OE2	GLU	2	B	3.07
8	188	SD	MET	21	A	<–	1976	N	ILE	1	B	3.34

to an immunogenic peptide fused on its surface. Expression of PMV CP in bacterial cell like (*E. coli*) leads to assembly VLPs. C-terminal fusion is not always efficient it depends on the character of the epitope fused to the efficient platform. And demonstrated by taking CTL-epitope attained from the NP (NucleoCapsid) of the influenza virus, fused to the carboxyl-terminal region of the PMV CP, leading to nanoparticles presenting surface-Displayed epitope. While the Papaya Mosaic Viral is put forward as a vaccine platform is clearly flexible and shown to tolerate the fusion of several immunogenic peptides to its C-terminus. This allows the displayed and expressed epitopes to freely adopt native conformations (Rioux et al. 2012).

Denis et al. reported earlier studied multimerization of the immunogenicity of Papaya Mosaic Viral like particles by fussing epitope of hepatitis-C virus and describe the engineering of PMV Capsid Protein as a carrier in addition to a Carboxyl-terminal fused with E2 epitope of hepatitis-C virus (Denis et al. 2007). The discovery of B-cell immunogenic epitopes is a crucial primary step for the advance of epitope peptide-based vaccines, diagnostic tools, and therapeutic antibodies. Immunogenic Epitope peptides can be displayed on the surface capsid protein subsequently those peptides assembled like virus particles act as vehicles for epitope display. Expression of immunogenic epitope peptides as fusions with surface loops of plant viral Capsid proteins has been used for the generation of several candidate animal vaccines (Hefferon 2018).

The Capripox viral envelop P32 protein multiple sequence alignment, amino acid sequences between each epitope and their homologous proteins showed that they were almost 100% conserved among 11 P32 immunogenic sequences. The identified immunogenic epitope peptides are Ep3- 110–118 regions of p32 envelop protein with peptide sequence ADIKNSENK, Ep6—regions between 11–19 of p32 protein with peptide sequence IVGREISDV and Ep8- 140–147 regions of p32 envelop protein with peptide sequence IEMQEKNI. These peptides are surface-displayed carboxyl and amino terminal regions of PaMV CP and identified the binding affinity each terminal regions. The binding capacity of immunogenic p32 epitope peptides with PaMV CP at Carboxy terminal (C) are EP3 (-55.6 ± 8.2), EP6 (-62.0 ± 5.2), EP8 (-52.4 ± 2.4) and the binding confirmation of epitope peptide displayed at C-terminus with Papayamosaic virus Capsid protein showed in Fig. 5. As well at amino-terminal (N) of PaMV CP are EP3 (-56.7 ± 4.8),

EP6 (− 55.4 ± 2.0) EP8(− 57.5 ± 2.1) and the binding confirmation of epitope displayed at N-terminus of Papayamosaic virus Capsid protein showed in Fig. 6. The three-dimensional structural modeled, identified analyzed epitopes were displayed on the surface of N and C terminals PMV CP. this will increase the perceptive of the P32 envelop protein structure and functions. And it may possibly place the foundation for the designing and development of a universal Capripox viral multi-epitope based peptide vaccine as well as detection antigen.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they donot have conflict of interest.

Animal and Human Participants This article dose not contain any studies with animal or human subjects performed by the authors.

Informed Consent Authors stated that there is no informed consent in the article.

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