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Homology modeling active site predictive of VP24 protein involved in Ebola Virus

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Abstract: Ebola is a single stranded RNA virus which has a filamentous structure and belongs to family of RNA virus called Filoviridae and genus *Ebolavirus*. Ebola virus causes severe hemorrhagic fever and is therefore a fatal disease in humans and non-human primates. Ebola viral protein (VP24) is a secondary matrix protein which has various roles in virulence of virus. VP24 interferes with the interferon signaling pathway by binding to karyopherin-α and blocking the Signal Transducers and Activators of Transcription (STAT-1) signaling pathway. In the present study we analyze protein sequence and predicted the 3 dimensional structure of VP24 protein using various bioinformatics tools. And we have also predicted the active/binding sites for the protein. These sites can be further use for the drug designing purpose for VP24 protein. It is thus involved in packaging of virus and in turn plays an important role in virulence. Since VP24 is present on the surface of viral envelope that has an affinity for plasma membrane. This protein is also essential for the replication of other proteins of virus as was suggested by Mateo *et al* and because of these reasons VP24 protein was selected for this study In this study Three dimensional structure predicted and validated by Swiss model and Ramachandran plot respectively. Our work suggests that VP24 protein can acts as target for the inhibition of Ebola virus. The further study of VP24 protein used in the molecular docking and structure based drug designing to inhibit in Ebola virus.

Introduction:

Ebola known as Ebola hemorrhagic fever is a rare and deadly disease caused by infection with one of the Ebola virus species. Ebola can cause disease in humans and nonhuman primates (monkeys, gorillas, and chimpanzees). Ebola is a single stranded RNA virus which has a filamentous structure and belongs to family of RNA virus called Filoviridae and genus *Ebolavirus*. There are five identified Ebola virus species, four of which are known to cause disease in humans: Ebola virus (*Zaire ebolavirus*); Sudan virus (*Sudan ebolavirus*); Taï Forest virus (*Taï Forest ebolavirus*, formerly *Côte d'Ivoire ebolavirus*); and Bundibugyo virus (*Bundibugyo ebolavirus*). The fifth, Reston virus (*Reston ebolavirus*), has caused disease in nonhuman primates, but not in humans. Ebola viruses are found in several African countries. Ebola was first discovered in 1976 near the Ebola River in what is now the Democratic Republic of the Congo. Since then, outbreaks have appeared sporadically in Africa. [1]

Ebola virus causes severe hemorrhagic fever and is therefore a fatal disease in humans and non-human primates. Ebola virus has a fatality rate of 90% in humans.the recent epidemic occurred in 2014 and affected multiple countries in West Africa and also a new case was reported on January 14, 2015 in Sierra Leone.5 Ebola virus can be transmitted by contact with infected person, vomits and also through sexual contact. [2]

The first symptoms of EHF are relatively unspecific and include a high fever with sudden Onset, headaches, muscle and joint pain and general malaise, as well as gastrointestinal symptoms such as diarrhea, nausea and vomiting. Hemorrhagic symptoms appear later in the course of disease (5 to 7 days after onset of symptoms) and most frequently occur in the gastrointestinal tract leading to hematemesis, hematochezia and melena. In contrast, overt bleeding, for example from venipuncture sites, is not as common, nor is intradermal bleeding. Death usually occurs between day 6 and 10 after onset of symptoms, and is caused by multi-organ failure and a syndrome resembling septic shock [2]

Ebola viral protein (VP24) is a secondary matrix protein which has various roles in virulence of virus. VP24 interferes with the interferon signaling pathway by binding to karyopherin-α and blocking the Signal Transducers and Activators of Transcription (STAT-1) signalling pathway.

Infection with Ebola virus blocks the production of alpha and beta interferon in the cell and thereby blocks the cells' response. Together with other viral proteins- Nucleoprotein (NP) and VP35, it is very necessary for the correct assembly and formation of functional nucleocapsids. It is thus involved in packaging of virus and in turn plays an important role in virulence.Since VP24 is present on the surface of viral envelope that has an affinity for plasma membrane. This protein is also essential for the replication of other proteins of virus as was suggested by Mateo *et al* and because of these reasons VP24 protein was selected for this study. [1]

After entry into the host cell, the EBOV envelope fuses with host cell membranes to release the nucleocapsid into the cytoplasm where transcription and replication take place. Initial transcription of the newly entered encapsidated RNA genome is entirely accomplished by the nucleocapsid proteins that are associated with the intruding virus (primary transcription). Transcription is regulated by conserved transcription start and stop signals at the viral gene borders (Nadine Biedenkopf *et al*). For transcription of the viral genome four viral proteins are essential: the nucleoprotein NP, the polymerase L, the polymerase cofactor VP35, and VP30. VP30 represents an essential Ebola virus-specific transcription factor whose activity is regulated via its phosphorylation state. Neither an approved vaccine nor antiviral therapy is available for humans.

The enveloped EBOV particle is composed of seven structural proteins, five of which form the helical nucleocapsid that represents the template for viral transcription and replication. The viral genome is encapsulated by the major nucleocapsid protein NP, and VP35, VP30, and VP24 interact with NP to form the mature nucleocapsid Transcription is regulated by conserved transcription start and stop signals at the viral gene borders. The gene start signals are part of RNA secondary structures, and it has been proposed that VP30 binds to the RNA at the first gene start signal to initiate transcription. Ebola viral protein 24 (eVP24) is considered a multifunctional secondary matrix protein present in viral particles. The broad roles eVP24 performs involve the formation of fully functional and infectious viral particles, promotion of filamentous nucleo capsid formation, mediation of host responses to infection, and suppression of the host innate immune system. It has been noted that VP24 function can overlap with that of two other viral proteins; eVP40 matrix protein which functions in virus budding, and eVP35 which is also associated with immune suppression VP24 disrupts the signaling pathway of STAT1. The STAT1 protein is phosphorylated by interferon's in response to viral infection

causing it to express a non-classical nuclear localization signal and bind to the importin protein karyopherin-α (KPNA). Once bound to KPNA, STAT1 is transported to the nucleus where it stimulates gene transcription in response to viral infection.

In the present study we analyze protein sequence and predicted the 3 dimensional structure of VP24 protein using various bioinformatics tools. And we have also predicted the active/binding sites for the protein. These sites can be further use for the drug designing purpose for VP24 protein.

Material and Methodology:

Protein Sequence retrieval and Primary analysis:

Protein sequence of protein minor nucleoprotein VP 24 was retrieved from Gene bank database. The physicochemical analysis were calculated by ProtParam tool (http://web.expasy.org/protparam/), including *pI*, total number of negatively and positively charged residues, the instability index (II), aliphatic index, and grand average of hydrophilic (GRAVY).

Structural Charecterization:

Similarity search was carried out by using BLAST software (https://blast.ncbi.nlm.nih.gov/Blast.cgi?PAGE=Proteins). SOPMA (Geourjon and Deléage, 1995)server(https://npsaprabi.ibcp.fr/cgi-bin/npsa_automat.pl?page=npsa_sopma.html). SOPMA is using homologue method of Levin *et al*. According to this method; short homologous sequence of amino acids will tend to form similar secondary structure. As well it also done by using Phyre2 (http://www.sbg.bio.ic.ac.uk/~phyre2/html/page.cgi?id=index) software and visualized by using Chimera (https://www.cgl.ucsf.edu/chimera/) software.

Homology modeling and Model evaluation:

Homology modeling was used for determining 3D structure of protein. Then, BLASTP was performed against PDB (Protein Databank, Bernstein *et al*., 1977) to retrieve the best suitable

templates for homology modeling. Preferred hit contains maximum identity and lowest e-value that it was used as a template. The modeling of the 3D structure of the protein was performed by using Swiss-Modeler (http://swissmodel. expasy.org/) program (Arnold *et al*., 2006; Bordoli *et al*., 2009).

Binding site Prediction:

The binding site of VP24 protein was predicted by RaptorX server (http://raptorx.uchicago.edu/BindingSite/). The binding site shows the small pockets of the tertiary structure where ligands bind to using the weak forces.

1] Organism : Zaire Ebolavirus

2] Protein : Ebola protein: VP24

3] Accession id: Gen Bank: ALX31300.1

4] Sequence:

>ALX31300.1 VP24 [Zaire ebolavirus]
MAKATGRYNLISPKKDLEKGVVLSDLCNFLVSQTIQGWKVYWAGIEFDVTHKGMALLHRLKTN
DFAPAWS
MTRNLFPHLFQNPNSTIESPLWAVRVILAAGIQDQLIDQSLIEPLAGALGLISDWLLTTNTNHFNM
RTQR
VKEQLSLKMLSLIRSNILKFINKLDALHVVNYNGLLSSIEIGTQNHTIIITRTNMGFLVELQEPDKS
AMN
RKKPGPAKFSLLHESTLKAFTQGSSTRMQSLILEFNSSLAI

5] Drug used:

I) **Plant name :** ***Andrographis paniculata*** / the **Kalmegh**

II) **Chemical compound : Andrographolide**

III) Drug id: ZZZLUK05 264212

IV) Related compounds with annotation:

1) Dihydroandrographolonide
2) Pacovatinin B
3) 3,14,19-tripropionylandrographolide
4) Andropanolide
5) calcaratarin D

Results and discussion:

Protein Sequence retrieval and Primary analysis

The physicochemical analysis of vp30 protein was performed using Protparam and results were shown in Table 1. Vp24 protein contains 251 amino acids with molecular weight 28201.81 Dalton and Theoretical pI 9.57.

Table 1. Physico-chemical properties of vp24 protein

Sr.No.	Parameters	Values
1	Molecular weight	28201.81D
2	Theoretical pi	9.57
3	Instability index	35.75
4	Extinction coefficients	31970
5	Total number of negatively charged residues (Asp + Glu):	19
6	Total number of positively charged residues (Arg + Lys):	26
7	Aliphatic index:	104.54
8	GRAVY -	-0.035

Protparam tool computed that the Vp24 protein is basic in nature and stable on the basis of parameters Theoretical pi and instability index. According to the GRAVY index protein is hydrophilic. The aliphatic index of a protein is 104.54 which defined as the relative volume occupied by aliphatic side chains (alanine, valine, isoleucine, and leucine). The total number of

positively charged residues (Arg+Lys 26) was found higher than the total number of negatively charged residues (Asp+Glu 19).

Structural Charecterization

The secondary structure of the protein was predicted using SOPMA server (Table 2 and Figure 1). It was observed that predominant with alpha helix (42.63%) followed by random coil (30.28%), and extended strand (18.33%). Random coils have important functions in proteins for flexibility and conformational changes such as enzymatic turnover (Buxbaum, 2007).

Table2. Secondary structure of vp24 protein using SOPMA

Sr.No.	Parameters	Values
1	Alpha Helix	42.63
2	Bita Sheets	8.76
3	Random coils	30.28
4	Extended strand	18.33

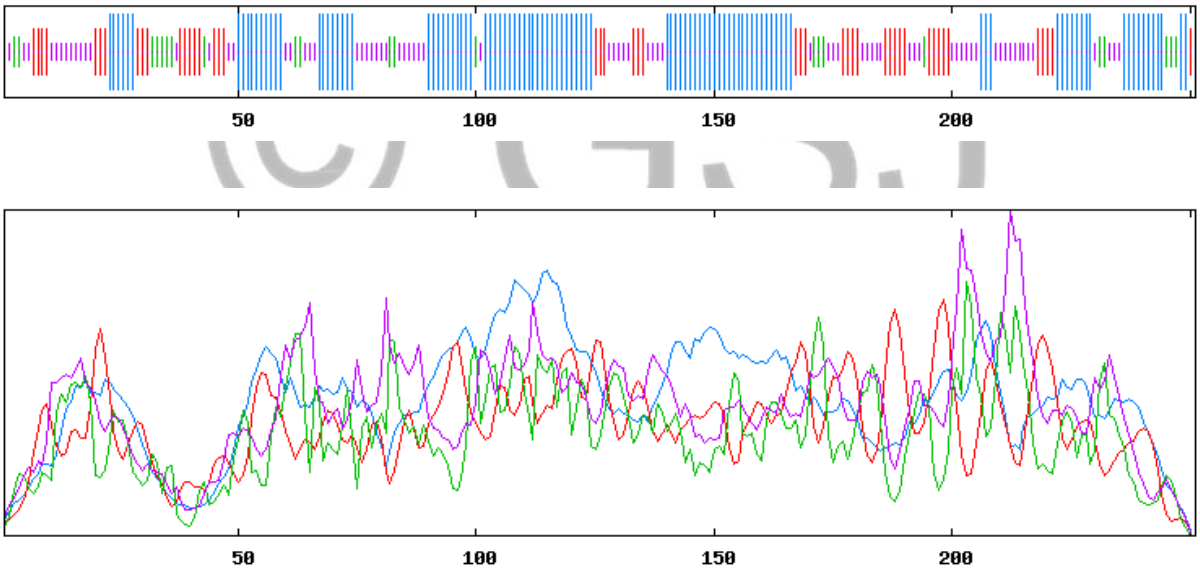
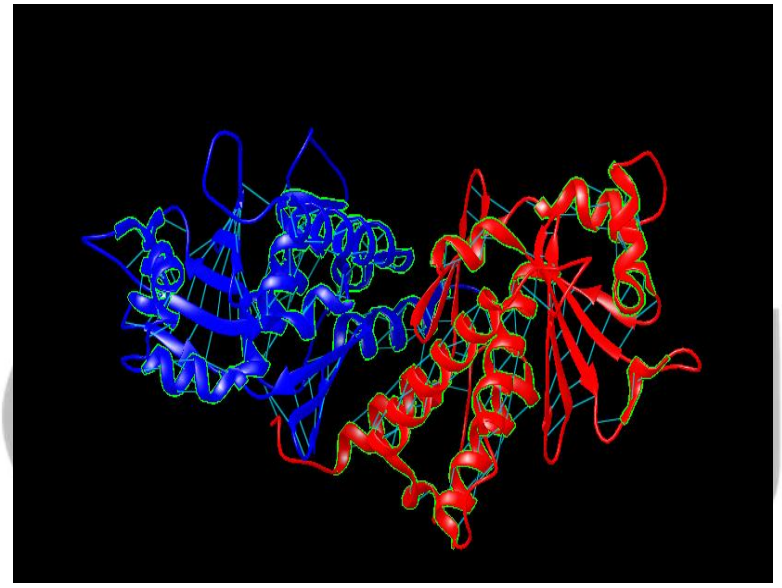


Figure 1. Secondary structure of vp24 protein using SOPMA

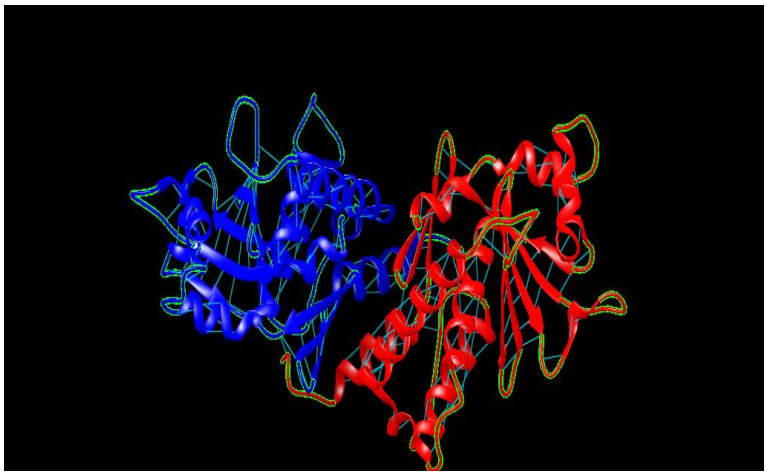
According to structure prediction by Phyre2 VP24 is known to antagonize interferon signaling by binding host karyopherin a proteins, thereby preventing them from transporting the tyrosine phosphorylated transcription factor STAT1 to the nucleus. Here, we report that VP24 binds STAT1 directly, suggesting that VP24 can suppress at least two distinct branches of the interferon pathway. Here, we also report the first crystal structures of VP24, derived from different species of ebolavirus that are pathogenic (Sudan) and nonpathogenic to humans

(Reston). These structures reveal that VP24 has a novel, pyramidal fold. A site on a particular face of the pyramid exhibits reduced solvent exchange when in complex with STAT1. This site is above two highly conserved pockets in VP24 that contain key residues previously implicated in virulence. These crystal structures and accompanying biochemical analysis map differences between pathogenic and nonpathogenic viruses, offer templates for drug design, and provide the three dimensional framework necessary for biological dissection of the many functions of VP24 in the virus life cycle.

Secondary structure with helix:



Secondary structure with coils:



Secondary structure with strand:

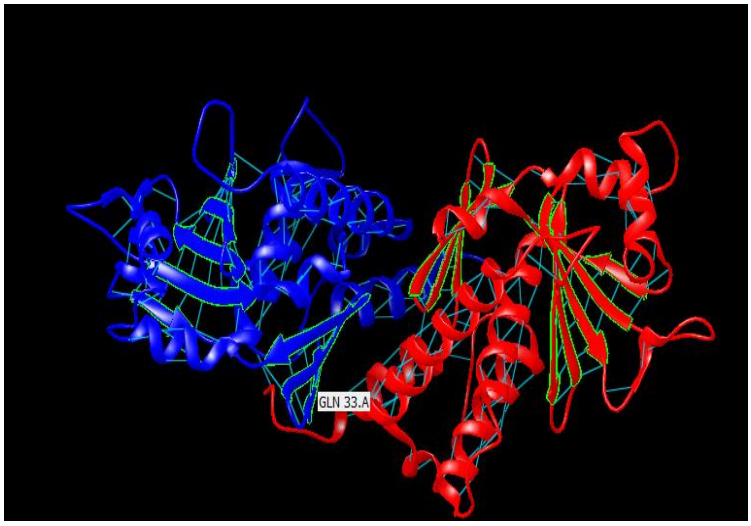
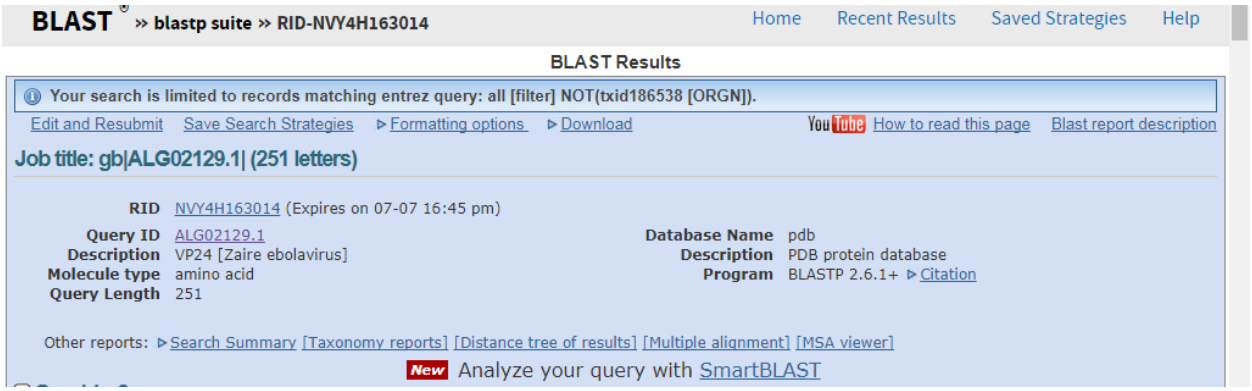


Figure 2. Secondary structure of vp24 protein using Phyre2.

Homology modeling and Model evaluation

The SWISS-MODEL homology modeling program was used for the predicting of three dimensional structures of the VP 24 proteins (Figure 4). BLASTP was performed against PDB (Protein Databank, Bernstein *et al*., 1977) to retrieve the best suitable templates for homology modeling. Preferred hit contains maximum identity and lowest e-value that it was used as a template PDBe 4m0q.1.A (Membrane-associated protein VP24) was selected as template with 99.12% sequence identity to query sequence. The quality and validation of the model was evaluated by Ramachandran plot analysis using PDBsumserver (Figure 5&6). Based on Ramachandran plot analysis **118** structures of resolution of at least **2.0** Angstroms and *R*-factor no greater than **20.0** a good quality model would be expected to have over **90%** in the most favoured regions(A,B,L) it also showed that only 0.2% residues in outlier region, 10.2% allowed region indicating that the models were of reliable and good quality.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Description VP24 [Zaire ebolavirus]
Molecule type amino acid
Query Length 251
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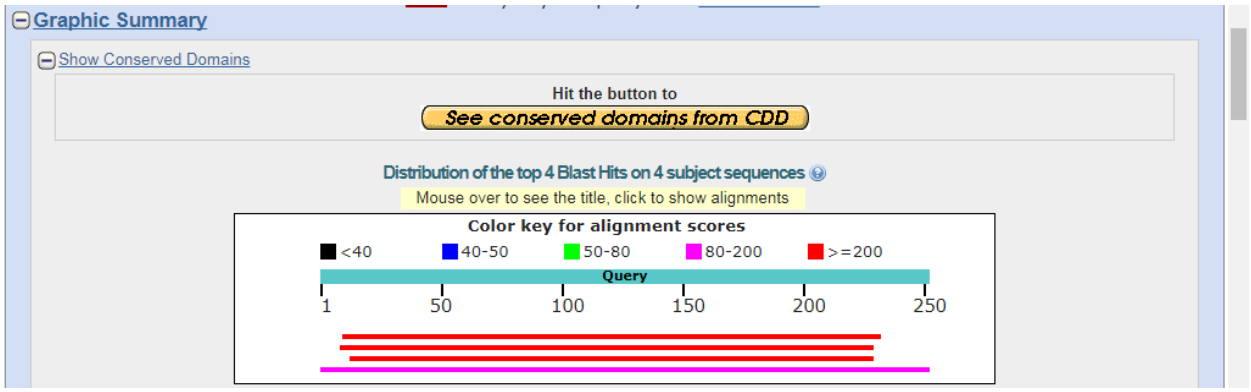
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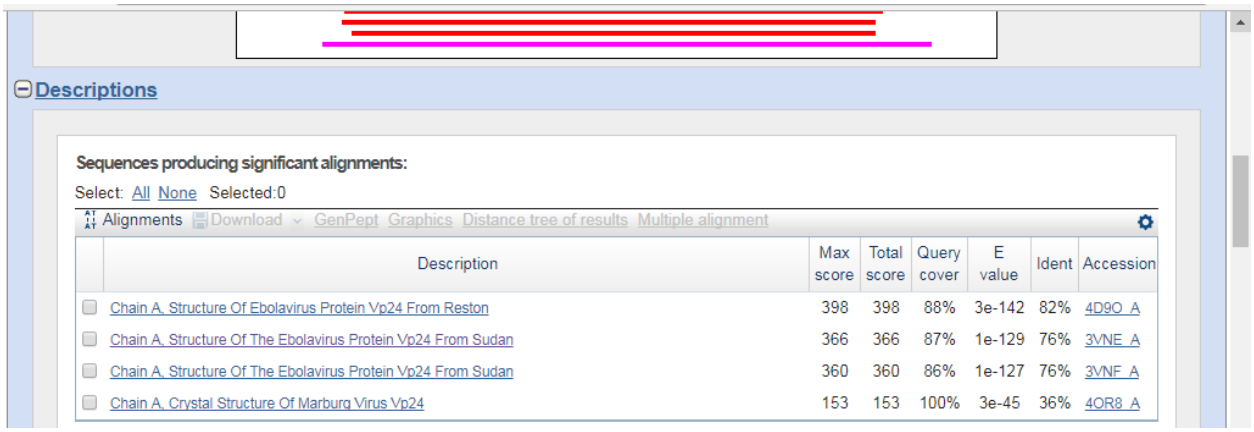
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Chain A, Structure Of Ebolavirus Protein Vp24 From Reston 398 398 88% 3e-142 82% 4D9O_A
Chain A, Structure Of The Ebolavirus Protein Vp24 From Sudan 366 366 87% 1e-129 76% 3VNE_A
Chain A, Structure Of The Ebolavirus Protein Vp24 From Sudan 360 360 86% 1e-127 76% 3VNF_A
Chain A, Crystal Structure Of Marburg Virus Vp24 153 153 100% 3e-45 36% 4OR8_A

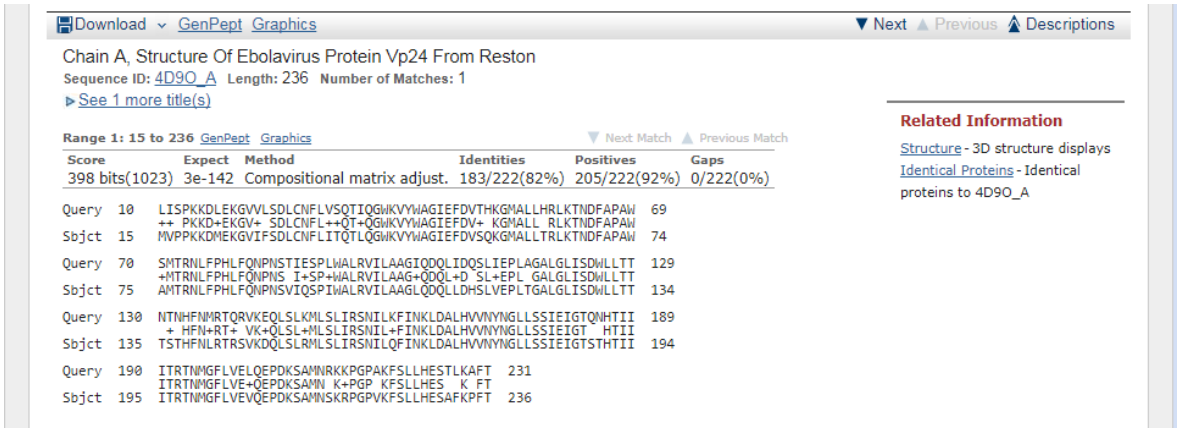

Figure 3. BLASTp of VP24 Protein

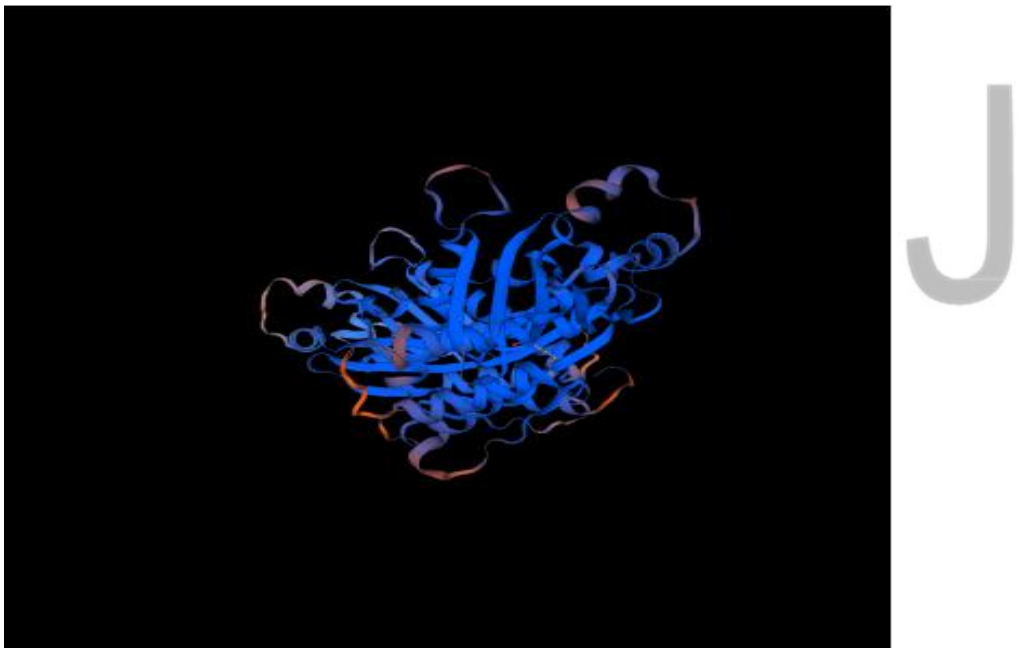

Figure 4. Predicted 3D structure of protein vp24 using SWISS-Model

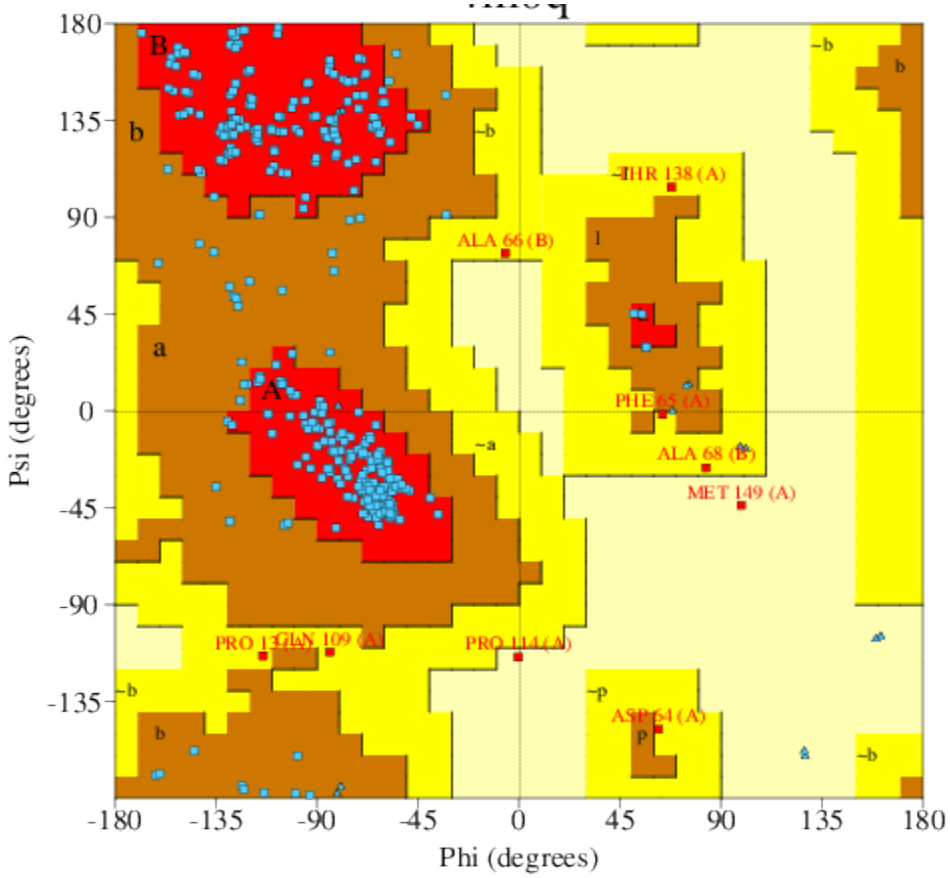

Figure 5. Ramachandran plot analysis

PROCHECK statistics

1. Ramachandran Plot statistics

		No. of residues	%-tage
Most favoured regions	[A,B,L]	352	88.0%*
Additional allowed regions	[a,b,l,p]	41	10.2%
Generously allowed regions	[~a,~b,~l,~p]	6	1.5%
Disallowed regions	[XX]	1	0.2%*
Non-glycine and non-proline residues		400	100.0%
End-residues (excl. Gly and Pro)		4	
Glycine residues		22	
Proline residues		18	
Total number of residues		444	

Figure 6. Procheck analysis

Binding site Prediction:

The predicted structure of VP24 protein was further studied for its binding site prediction at PDBsum server. This server predicted that predicted structure contains one hundred and two binding sites. As described in fig7.

	PDB code	Model	Length	%-tage identity	a.a. overlap	z-score	Ligands	Protein name
1.	4m0p(A)	X-ray 1.92Å	222	98.6%	222	1884.7		Ebola virus vp24 structure
2.	6ehm(C)		222	98.6%	222	1884.7		Model of the ebola virus nucleocapsid subunit from recombinant virus- like particles
3.	4u2x(A)	X-ray 3.15Å	216	99.1%	216	1838.9		Ebola virus vp24 in complex with karyopherin alpha 5 c-terminus
4.	3vne(A)	X-ray 2.00Å	218	73.6%	220	1472.3		Structure of the ebolavirus protein vp24 from sudan
5.	4d9o(A)	X-ray 2.00Å	202	73.9%	222	1361.1		Structure of ebolavirus protein vp24 from reston
6.	3vnf(A)	X-ray 2.10Å	199	70.4%	216	1001.2		Structure of the ebolavirus protein vp24 from sudan
7.	4or8(B)	X-ray 2.65Å	226	37.1%	232	649.4		Crystal structure of marburg virus vp24
8.	4or8(A)	X-ray 2.65Å	225	37.1%	232	641.6		Crystal structure of marburg virus vp24
9.	3eb8(A)	X-ray 2.40Å	334	27.2%	114	123.7		Vira
10.	5wug(A)	X-ray 2.80Å	158	33.9%	62	123.7		Crystal structure of sigw in complex with its anti-sigma rsi binding form
11.	3or9(A)	X-ray 1.60Å	194	23.9%	155	123.6	ACT, MES.	A tandem sh2 domain in transcription elongation factor spt6
12.	3ejp(A)	X-ray 1.60Å	194	23.9%	155	123.6	ACT, MES.	A tandem sh2 domain in transcription elongation factor spt6 binds the phosphorylated RNA polymerase ii c-terminal repeat domain(ctd)
13.	4j2o(F)	X-ray 2.65Å	300	23.6%	208	123.2	NAP.	Crystal structure of NADP-bound wbjb from a. Baumannii community strain d1279779
14.	5wur(A)	X-ray 2.60Å	157	37.7%	61	121.2		Crystal structure of sigw in complex with its anti-sigma rsi oxdized form
15.	5n6a(A)	X-ray 3.10Å	710	32.5%	80	121.0	ADP, PO4, GOL.	Cardiac muscle myosin motor domain in the pre-powerstroke state
16.	5mmi(F)		193	19.3%	150	121.0	__C-__A.	Structure of the large subunit of the chloroplast ribosome
17.	2bpo(A)	X-ray 2.90Å	641	26.1%	230	119.1	FAD, FMN, NAP, SO4.	Crystal structure of the yeast cpr triple mutant: d74g, y75f, k78a.
18.	2bn4(A)	X-ray 2.91Å	643	26.1%	230	119.1	FAD, FMN, NAP.	A second fmn-binding site in yeast NADPH-cytochrome p450 reductase suggests a novel mechanism of electron transfer by diflavin reductase
19.	2bf4(A)	X-ray 3.00Å	645	26.1%	230	119.1	FAD, FMN, NAP, SO4.	A second fmn-binding site in yeast NADPH-cytochrome p450 reductase suggests a novel mechanism of electron transfer by diflavin reductases.
20.	5mlc(G)		179	19.1%	136	118.9		Cryo-em structure of the spinach chloroplast ribosome reveals the location of plastid-specific ribosomal proteins and extensions
21.	6f0l(5)		634	20.0%	220	117.9	ADP.	S. Cerevisiae mcm double hexamer bound to duplex DNA
22.	3gxw(C)	X-ray 1.90Å	100	25.0%	60	117.8	SIN.	Structure of the sh2 domain of the candida glabrata transcription elongation factor spt6, crystal form a
23.	5x8t(F)		175	19.4%	134	115.1		Structure of the 50s large subunit of chloroplast ribosome from spinach
24.	5h1s(H)		175	19.4%	134	115.1		Structure of the large subunit of the chloro-ribosome
25.	3bbo(H)		175	19.4%	134	115.1		Homology model for the spinach chloroplast 50s subunit fitte cryo-em map of the 70s chlororibosome
26.	2gai(A)	X-ray 1.70Å	581	23.7%	186	113.2		Structure of full length topoisomerase i from thermotoga maritima in triclinic crystal form
27.	2gai(A)	X-ray 1.95Å	581	23.7%	186	113.2		Structure of full length topoisomerase i from thermotoga maritima in monoclinic crystal form
28.	2hkl(A)	X-ray 2.50Å	164	33.8%	74	113.0	EDO.	Structural genomics, the crystal structure of a putative transcriptional regulator yggd from shigella flexneri 2a str. 2457t
29.	4zdu(A)	X-ray 2.30Å	416	34.7%	49	111.7		Crystal structure of importin-alpha bound to a non-classical nuclear localization signal of the influenza a virus nucleoprotein
30.	4uaf(B)	X-ray 1.70Å	425	34.7%	49	111.5	PO4.	Importin alpha 1 delta ibb in complex with influenza pb2 nuclear localization domain
31.	5ctt(A)	X-ray 1.70Å	426	34.7%	49	111.5		Crystal structure of human sart3/tip110 nls-mouse importin alpha complex
32.	4yi0(C)	X-ray 1.81Å	425	34.7%	49	111.5		Structure of mouse importin a1 bound to pom121nls
33.	4fds(B)	X-ray 1.88Å	426	34.7%	49	111.5	SER-LYS-ARG-ALA-ARG-PRO-ALA.	Structure of importin-alpha: dutpase s11e nls mutant complex
34.	4mz6(E)	X-ray 1.88Å	426	34.7%	49	111.5	SER-LYS-ARG-ALA-ARG-PRO-ALA, GLU-PRO-SER-LYS-ARG-ALA-ARG-PRO-ALA-GLU.	Structure of importin-alpha: dutpase s11e nls mutant complex
35.	3ul1(B)	X-ray 1.90Å	426	34.7%	49	111.5		Mouse importin alpha: nucleoplasmin cnls peptide complex
36.	5d5k(C)	X-ray 1.90Å	424	34.7%	49	111.5		Crystal structure nls from human parp-2 complexed with importin alpha delta ibb
37.	5umz(B)	X-ray 1.90Å	426	34.7%	49	111.5	LYS-LYS-ARG-ARG-ARG-GLU, GLY-LYS-LYS-ARG-ARG-ARG-GLU-ARG, GOL.	Structure of tnrc6a nls in complex with importin-alpha
38.	5huw(C)	X-ray 1.95Å	423	34.7%	49	111.5	GLY-PRO-PRO-LYS-LYS-ARG-	Structure of hsv-1 large terminase nls bound to importin alpha

39.	4u5u(A)	X-ray 1.96Å	426	34.7%	49	111.5	3D2.	Importin-alpha minor nls site inhibitor
40.	4u5v(A)	X-ray 1.97Å	426	34.7%	49	111.5	RH2.	Importin-alpha minor nls site inhibitor
41.	5huy(C)	X-ray 1.98Å	423	34.7%	49	111.5	ALA-THR-ARG-LYS-ARG-PRO-ARG, ALA-THR-ARG-LYS-ARG-PRO-ARG-ARG-ALA.	Structure of hcmv small terminase nls bound to importin alpha
42.	3oqs(A)	X-ray 2.00Å	425	34.7%	49	111.5	VAL-ALA-LYS-LYS-TYR-ARG-ASN.	Crystal structure of importin-alpha bound to a clic4 nls peptide
43.	3ul0(B)	X-ray 2.00Å	426	34.7%	49	111.5		Mouse importin alpha: mouse cbp80y8d cnls complex
44.	3zin(A)	X-ray 2.00Å	426	34.7%	49	111.5	GLN-LYS-ARG-SER-PHE-SER.	Gu_alpha_helicase
45.	4u5o(A)	X-ray 2.00Å	426	34.7%	49	111.5	3D5.	Importin-alpha minor nls site inhibitor
46.	5ekf(A)	X-ray 2.00Å	425	34.7%	49	111.5	SER-LEU-LYS, ARG-LYS-ARG, SER-SER-SER-LEU-LYS-ARG-LYS-ARG-LEU-SER.	Crystallization and x-ray diffraction data collection of importin-alpha from mus musculus complexed with a xpg nls peptide, fragment 1
47.	5svz(A)	X-ray 2.00Å	426	34.7%	49	111.5	GLY-ARG-LYS-LYS-ARG-ARG-GLN-ARG.	HIV-1 tat nls in complex with importin alpha
48.	5wum(A)	X-ray 2.00Å	426	34.7%	49	111.5	GLU-LYS-ARG-PRO-ARG-SER-PRO-SEP, GLU-LYS-ARG-PRO-ARG-SER.	Crystal structure of mouse importin-alpha1 bound to s385-phosphorylated nls of ebna1
49.	3tpm(A)	X-ray 2.10Å	422	34.7%	49	111.5		Crystal structure of mal rpel domain in complex with importin-alpha
50.	3ukw(B)	X-ray 2.10Å	426	34.7%	49	111.5	BTB.	Mouse importin alpha: bimax1 peptide complex
51.	3zio(A)	X-ray 2.10Å	426	34.7%	49	111.5	ARG-LYS-ARG-GLY-TYR-SER-VAL-ALA-PHE, ARG-LYS-ARG-GLY-TYR-SER.	Minor-site specific nls (a28)
52.	3zip(A)	X-ray 2.10Å	426	34.7%	49	111.5	ARG-LYS-ARG-LYS-PHE-SER, HIS-ARG-LYS-ARG-LYS-PHE-SER-ASP-ALA-	Minor-site specific nls (b6)

Conclusion

The VP24 protein is involve in the transcription of Ebola virus. The present study we analyzed the physicochemical properties of VP24 protein by using Protparam tool. The 3D structure of protein was predicted using SWISS MODEL server. The final model was further evaluated by using Procheck and Ramachandran plot analysis. Binding site of the protein was studied using PDBsum database. From the present study it has been concluded that VP24 protein can be used as target for the inhibition of Ebola virus. The molecular structural insight encompasses to the development of new drug for inhibition VP24 protein.

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