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Review article

In silico designing of putative peptides for targeting pathological protein Htt in Huntington's disease

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ABSTRACT

Huntington's disease is a neurodegenerative disease caused by CAG repeat in the first exon of HTT (Huntingtin) gene, leading to abnormal form of Htt protein containing enlarged polyglutamine strands of variable length that stick together to form aggregates and is toxic to brain causing brain damage. Complete reversal of brain damage is not possible till date but recovery may be possible by peptide therapy. The peptide-based therapy for Huntington's disease includes both poly Q peptide as well as non poly Q peptides like (QBP1)2, p42, Exendin 4, ED11, CaM, BiP, Leuprorelin peptide. The novel approach that is currently being tested in this article is the peptide-based therapy to target the mutated protein. This approach is based on the principle of preventing the aggregation of mutant Htt by blocking the potential sites responsible for protein aggregation and thereby ameliorating the disease symptoms. Herein, we have screened a variety of potential peptides that were known to prevent the protein aggregation, comparatively analyzed their binding affinity with homology modeled Htt protein, designed novel peptides based upon conservation analysis among screened potential peptides as a therapeutic agent, comparatively analyzed the therapeutic potential of novel peptides against modeled Htt protein for investigating the therapeutic prospects of Huntington's disease. We have designed a peptide for the therapy of Huntington's disease by comparing several peptides, which are already in use for Huntington's disease.

1. Introduction

A growing body of evidence has reported the occurrence of tri nucleotide repeat neurological disorders, such as polyglutamine disorders that include Huntington's disease (HD), dentatorubralpallidoluysian atrophy (DRPLA), spinal-bulbar muscular atrophy (SBMA), and six spinocerebellar ataxias (SCA 1, 2, 3, 6, 7, and 17). These triplets repeat expansion diseases (TREDs) are divided into two classes i.e. coding and non-coding, based on the localized region of trinucleotide repeats. For instance, Polyglutamine (polyQ) diseases are one of the coding trinucleotides repeat disorders caused by CAG repeat expansions coding abnormal polyglutamine stretch in mutant protein. However, the physical symptoms appear usually between 35 to 44 years of age but can also observe earlier in life in the successive generations [1, 2]. This polyglutamine extension affects protein trafficking in specific cellular compartments where it stimulates protein aggregation and triggers neuronal cell death [3].

Among the above mentioned nine PolyQ disorders, Huntington's disease is one of the prominent adult-onset polyQ disorders that is marked by disturbed muscle coordination, mental decline and behavioral changes. With the progression of disease, uncoordinated bodily movements are more evident, along with increased mental and physical disabilities, and other behavioral symptoms [4]. Moreover, progression of disease onsets other problems like pneumonia, physical injury and heart diseases that reduces the life expectancy by twenty years from the age of its commencement. Researchers have identified the autosomal dominant genetic mutation in first exon of huntingtin gene, which is responsible for the disease progression [5]. The mechanism associated with the damaged caused by the abnormal/mis-folded proteinaggregate is not crystal clear but still some aggregate studies have been performed by software analysis. Normally, Htt protein contains 6–35 glutamine residues while more than 36 repeats are found in case of diseased state [6].

Amongst the proposed mechanism for protein aggregation till date are ubiquitin-proteasomal degradation, autophagy, transcriptional dysregulation, neuronal inflammation, mitochondrial dysfunction to determine the outline of observed neuronal dysfunction and cell death. It has been seen that alterations in certain specific cellular pathways share a common pathophysiology of polyQ disorders. Such pathways include

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transcriptional regulation, mitochondrial function and cellular proteostasis. Based on the proposed mechanisms, a number of therapeutic approaches have been identified such as ubiquitin-proteasomal degradation [7], RNA therapy; chaperon mediated HSP 70/HSP 90 therapy (Heat Shock Protein), caspase targeted therapy, crispr/cas9 based therapy and peptide based therapies are existing modes of therapy that improves the symptoms of the disease. Since there are no precise therapeutic strategies available for Huntington's Disease (HD) treatment, the current treatment strategies have shown improvements, mainly in motor functions in HD brain [8, 9, 10, 11]. We aim to design novel peptide-based therapeutics *in silico* method by comparing the existing peptides.

Till the date, amongst the peptide therapy used for Huntington's disease is QBP1 (Poly Q binding peptide), p42, ED11, Exendin4, BIP. These peptides (QBP1 and p42) targets the N terminal of Htt protein and prevents aggregation while ED11 targets caspase 6. The Htt protein has binding site for proteins like caspase 3, calpain, p42 peptide. The p42 binds on 480 residues to 502 residues while QBP 1 binds on other sites in N terminal region of Htt protein. Herein, we have compared peptide-based (ED 11, Exendin-4, CaM, QBP1, BIP) therapeutic approach for targeting the aggregate prone areas in Htt protein, that can decelerate the progression of disease [12, 13, 14]. QBP1 and p42 targets poly Q disease, ED11 targets caspase 6 but is used in Huntington's therapy. Exendin 4 is an anti-diabetic as well as anti-Huntington's disease therapeutic peptide. CaM peptide is also anti-huntingtin. Hence, all peptides targets different protein of different therapeutic value and treats disease.

In this article, we have compared the sequence of all peptides and designed a new peptide for Huntington's therapy. The new peptide has been characterized and predicted for its structure and compared by protein-peptide docking, structure and toxicity for its efficacy. The novel peptide is tryptophan rich and possessed the good properties of existing peptides for delivery.

2. Methodology: docking of Htt with existing peptides and newly designed peptides

2.1. Screening of potential peptides

The potential peptides have been screened through literature that was known to slow down or stop the disease progression via targeting toxic pathogenic protein aggregates. Based on the researches carried out in various studies regarding peptide-based therapy, different approaches have been identified to target toxic proteins. Moreover, the peptide sequence has been compiled together in FASTA format.

2.2. Target protein preparation

Target protein preparation involved the identification of attachment sites for mutant protein responsible for aggregation. based on the information about aggregation sites, huntingtin (htt) protein has been homology modeled for the site of protein aggregation using swiss-model bioinformatics tool (https://swissmodel.expasy.org/) [15, 16, 17, 18]. further, the homology model was validated using homology modeling tools called saves (procheck, errat, verify_3d, prove, rampage) and the best model was identified. the pdb no used for n terminal of htt was pdb 3106.

2.3. Model validation

Procheck: It analyzes the residue-by-residue geometry and overall structure geometry, and thus it checks the stereochemical quality of a protein structure [19, 20]. Errat: It plots the value of the error function versus position of a 9-residue sliding window by analyzing the statistics of non-bonded interactions between different atom types, from highly refined structures; calculation is done through a comparison with statistics [21]. Verify_3d: by assigning a structural class on the basis of its location and environment (alpha, beta, loop, polar, nonpolar etc), compatibility of an atomic model (3d) is determined with its own amino acid sequence (1d) [22,23]. Prove: it uses an algorithm to calculate the volumes of atoms in macromolecules and then calculate z-score deviation of the model from pdb-structures having high resolution (2.0 å or better) [24]. Rampage: It depicts the residues lying in allowed and disallowed regions (http://mordred.bioc.cam.ac.uk/~rapper/rampage.php). Thus, the best obtained model was used for docking studies with the peptides chosen for investigation.

2.4. Protein peptide docking

Protein–peptide interactions are essential for enabling the atomic-level understanding of protein interactions. Here, the prepared peptides were docked with best obtained Htt protein using CABS dock tool (http://biocomp.chem.uw.edu.pl/CABSdock) [25, 26]. CABS-dock is a structural prediction tool which is used for predicting protein-peptide interactions. The docking is performed by searching templates from the protein data bank of experimentally determined structures, and the models are generated using energy-based optimization techniques. The obtained results were analyzed, and best affinity binding peptides have been identified.

2.5. Novel peptide designing

The novel peptide has been designed based on the conservation pattern among best obtained docking results with the target protein using Bioedit software for multiple alignment of existing peptide.

2.5.1. Conservation analysis and de novo peptide designing

The sequence conservation analysis has been done between different peptides using “Bioedit” software to determine the sequence homology among peptides. Further based on the homology results conserved residues were identified, which were used for designing novel possible peptides using different combinations. Thus, designed potential therapeutic peptides were preceded for docking studies for validating their binding potential. Hence obtained the best peptide may mimic as an inhibitor for toxic Htt protein aggregation thereby ameliorating the symptoms in HD patients.

3. Result

3.1. Role of mutant Htt in Huntington's disease

The Huntington's disease is a result of mutated Htt gene due to extra number of CAG repeats leading to neuron degeneration (see Figure 1).

3.2. Screening of peptides used in Huntington's disease

The literature mining has been done to screen the potential peptides responsible for preventing the aggregation of neurotoxic proteins in HD which have been summarized in Table 1. These peptides have been used earlier in the peptide-based researches. These peptides bound to their therapeutic targets and prevented aggregation of the proteins or the misfolding of proteins.

The presence of tryptophan is important in preventing aggregates as it has been shown that in QBP1 peptide 11 amino acid can be easily shortened to 8 amino acid by retaining tryptophan rich motif in the peptide to inhibit polyglutamine aggregation. Moreover, the presence of the large number of tryptophan stabilizes the peptide.

3.3. Target Htt protein preparation for docking with peptide

3.3.1. Homology modeling results

The homology modeling results for Htt protein has been summarized based on overall quality factor, 3D-1D score and the number of residues in favored region Model 3 (Figure 2) was predicted to be the best model.

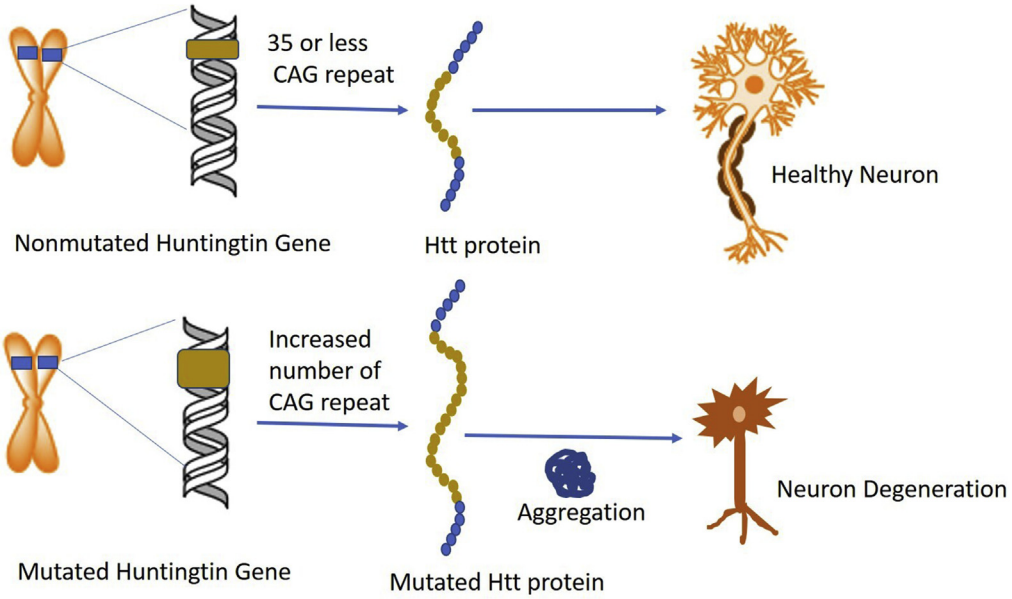

Figure 1. Increased number of CAG repeats leading to Huntington's disease: The peptide therapy helps to reduce its symptoms and hence potential existing peptides preventing the mutant protein aggregation have been investigated and new peptide designed.

Table 1. List of potential peptides preventing mutant protein aggregation.

S.NO.	POTENTIAL PEPTIDE	PEPTIDE SEQUENCE	THERAPEUTIC TARGET	REFERENCES
1	QBP1	SNWKWWPGIFD	polyQ aggregation	[27]
2	CaM peptide	MKDTDSEEEIREAFRVFDKDGNGYISAAELRHVMTNLGEKLTDEEV (A fragment of CaM, residues 76–121)	Aberrant interaction between Htt and CaM	[28, 29, 30]
3	BIP	VPMLK/VPTLK	Bax-induced apoptosis	[31, 32]
4	Exendin-4	HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS	Abnormal energy Metabolism	[33]
5	Leuprorelin	Pyr-HWSYLLRP-NHEt	Nuclear accumulation	[34, 35, 36, 37]
6	P42	AASSGVSTPGSAGHDIITEQPRS	N17 domain of htt	[38]
7	(QBP1)2	SNWKWWPGIFDSNWKWWPGIFD	Expanded polyQ stretch	[39, 40]
8	ED11	GRKKRRQRRRPPQSSEIVLDGTDN	Inhibitor of caspase-6	[41]

The homology validation results were based on three generated models with G-factor 0.06, 0.01 and 0.19 with overall quality factor of 90, 91 and 96. Good resolution structure produce quality factor more than 95%.

3.3.2. Protein peptide docking

All the peptides were docked with Model 3 using CABS-dock tool and the Energy values (receptor energy, ligand energy, interaction energy and total energy) generated after docking are depicted. A total of 10 models were obtained that were compared based on the total energy. The minimum energy values model (best model) of target peptides has been highlighted in the table. The best model results obtained from each peptide are listed in Table 2. A default value of 1.4 Å distance was used from catalytic pocket was used.

The potential therapeutic peptides based on the minimum total energy are Exendin-4 and ED11. Moreover, the docking results of both peptides with modeled Htt are shown in Figure 3. Here, (QBP1) 2, CaM, Exendin-4, ED11, Leuprorelin and P42 are found to bind at the active site pocket whereas BIP and QBP1 interact away from the active site region. Among them, Exendin-4 and ED11 are found to have minimum binding scores i.e. -2129.88 kcal/mol and -2184.63 kcal/mol respectively.

3.3.3. Conservation analysis

The conservation analysis has been done among the potential peptides identified through the literature survey as shown in Figure 4. The sequence similarity between the peptides has been identified at 60% significance using a multiple sequence alignment tool in BIOEDIT software. Here the key residues Lysine (K), Tryptophan (W), Arginine (R), Leucine (L) are found to be conserved and important for preventing the protein aggregation.

The presence of tryptophan is important in preventing aggregates as it has been shown that in QBP1 peptide 11 amino acid can be easily shortened to 8 amino acid by retaining tryptophan rich motif in the peptide to inhibit polyglutamine aggregation. Moreover, presence of the large number of tryptophan stabilizes the peptide. Hence four new peptide retains the tryptophan in the peptide sequence, and two are different sequence for further screening.

3.3.4. De novo peptide designing

The novel peptides are formulated by taking Exendin-4 and ED11 as test peptides and inserting conserved amino acid residues based on the information about key conserved residues for designing different combinations of novel peptides as depicted in Table 3.

The analysis of these peptides from the available software (Pasta) for aggregation of peptide predicted that NP_1 and other designed peptide does not form self aggregates as compared to existing peptides and others from Pasta while Tango demonstrates different result.. Pasta: Prediction of amyloid structural aggregates. O amyloid was predicted for all newly designed peptide while the negative energy was low for NP_5 and NP_6. Tango:NP_1 to NP_4 has aggregating tendency based on identified sequence while NO_5 and NP_6 has no aggregating tendency based on the new designed peptide as well as compared to established peptide result. When the results of Tango and Pasta is compared with already known

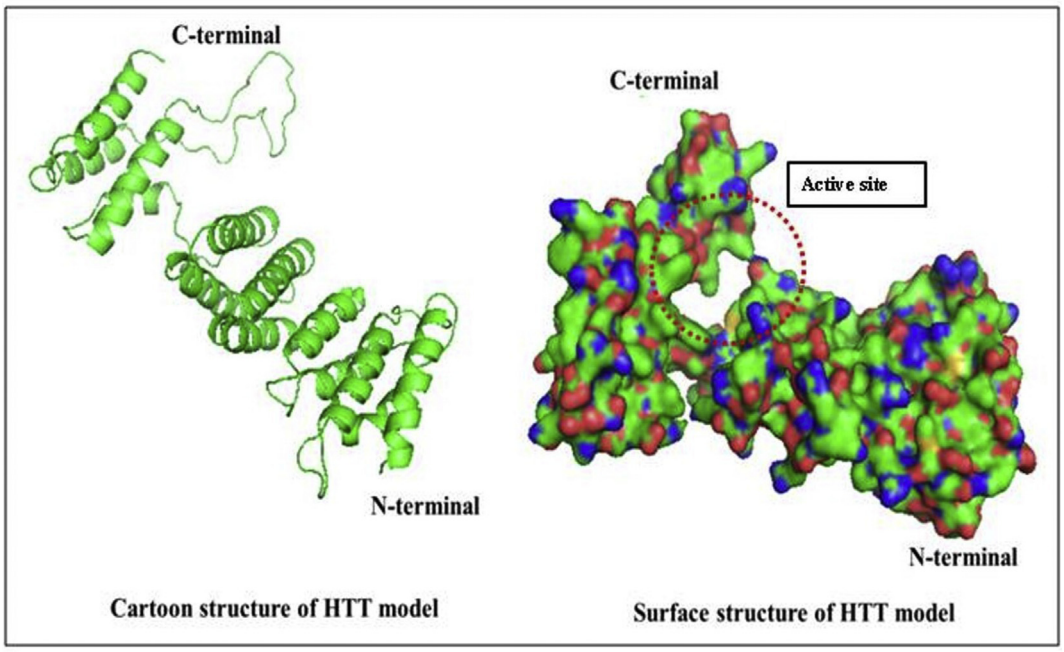

Figure 2. Best HTT model 3 depicting their cartoon and surface structure: The crystal structure for 449 residues have been generated and the N-terminal indicates the N terminal of 449 residue in Htt exon 1, while C-terminal is the C terminal of 449 residue in Htt exon 1. The active site is the active site of 449 residue in Htt exon 1 for its interaction with the peptide. Note: The dotted circle indicates the active site.

Table 2. Best docked models from each peptide.

S.No.	Peptide Name	Model No.	Ereceptor (kcal/mol)	Eligand (kcal/mol)	Einteraction (kcal/mol)	Etotal (kcal/mol)
1	(QBP1)2	5	-1672.83	-73.56	0	-1746.39
2	BIP	10	-2078.13	-3.65	0	-2081.78
3	CaM	9	-2055.07	-41.93	0	-2097
4	**ED11**	**2**	**-2026.09**	**-158.54**	**0**	**-2184.63**
5	**Exendin-4**	**9**	**-1907.59**	**-155.69**	**-66.6**	**-2129.88**
6	Leuprorelin	2	-1938.36	-8.78	0	-1947.14
7	P42	3	-1999.77	-52.12	0	-2051.89
8	QBP1	10	-2004.34	-31.37	0	-2035.71

Note: The minimum negative energies have been highlighted in bold.

Table 3. Established peptide and novel potential peptide designed sequences.

S.NO.	POTENTIAL PEPTIDE	PEPTIDE SEQUENCE	Tango Amylogenic region	Pasta amyloid aggregate prediction
1	QBP1	SNWKWWPGIFD	No	0
2	CaM peptide	MKDTDSEEEIREAFRVFDKDGNGYISAAELRHVMTNLGEKLTDEEV (A fragment of CaM, residues 76–121)	No	
3	BIP	VPMLK/VPTLK	No	
4	Exendin-4	HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS	No	
5	Leuprorelin	Pyr-HWSYLLRP-NHEt	No	
6	P42	AASSGVSTPGSAGHDIITEQPRS	No	0
7	(QBP1)2	SNWKWWPGIFDSNWKWWPGIFD	No	
8	ED11	GRKKRRQRRRPPQSSEIVLDGTDN	No	

S.NO.	NOVEL PEPTIDE NAME	SEQUENCE	Tango Aggregating region	Pasta Amyloid region
1	NP_1	LSRQMEESNVRWWIEWLRSGGPSLGGPPS	VRWWIEWLR(96)	0 (-4.5)
2	NP_2	LSRQMEESNVRWWIEWLQSGGPSLGGPPS	VRWWIEWLQS(96)	0 (-4.5)
3	NP_3	LSRQMEESSVRWWIEWLQSGGPSLGGPPS	VRWWIEWLQS(96)	0 (-4.5)
4	NP_4	LSRQMEESSVRWWIEWLRSGGPSLGGPPS	VRWWIEWLR(96)	0 (-4.5)
5	NP_5	GESKRKQRRRPPRNSEIVLGGTDS	No	0 (-3.3)
6	NP_6	GESKRKQRRRPPKNSEIVLGGTDS	No	0 (-3.3)

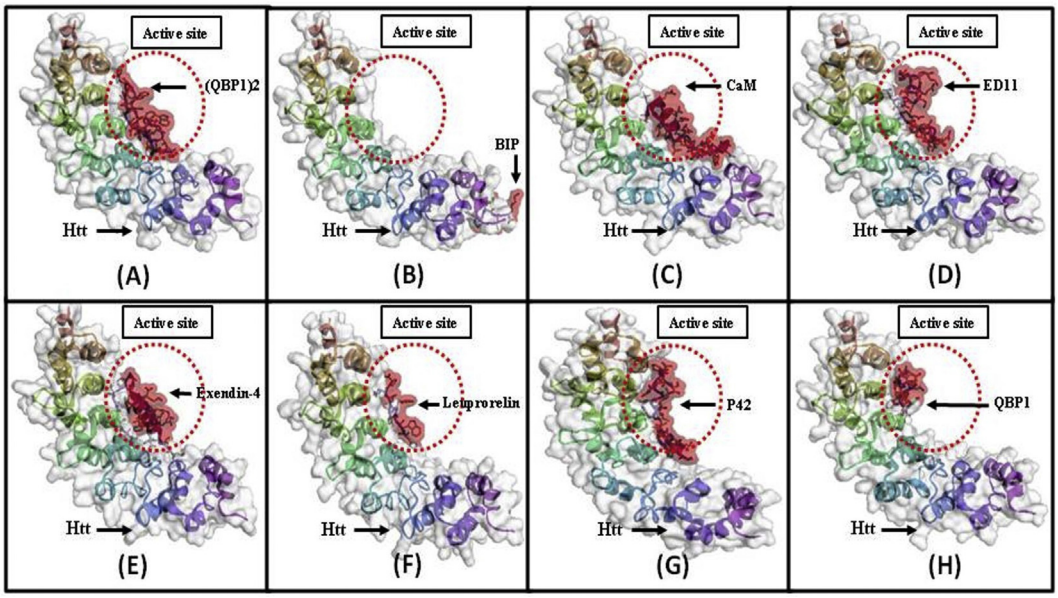

Figure 3. The figure shows docked structures of (A) (QBP1)2, (B) BIP, (C) CaM, (D) ED11, (E) Exendin-4, (F) Leuprorelin, (G) P42, (H) QBP1 with HTT model. Note: The dotted circle indicates the active site.

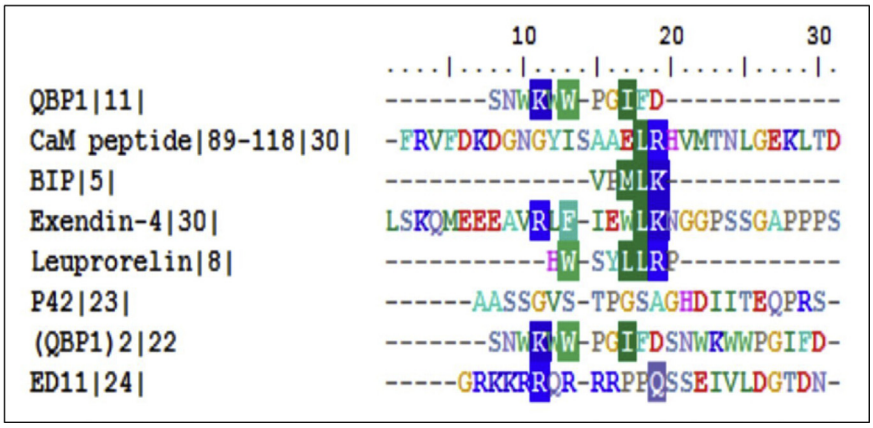

Figure 4. Multiple sequence alignment of different potential peptides inhibiting aggregation of proteins.

peptides, then the known peptides demonstrates no amyloidic region both from Pasta and Tango. Hence, these newly designed peptides is in general not aggregate forming but may be checked for further analysis.

3.3.5. Protein peptide docking

The results obtained from CABS-dock proved that some of the novel peptides designed has lower total energy values, thereby signifying the potential affinity of novel peptides in slowing down/inhibiting the aggregation of mutated Htt protein. The docking results of novel peptides have analysed while the combined summary results of best novel peptide models are shown in Table 4.

The docking results proved that the novel peptides formed were more effective in inhibiting the aggregation of HTT protein than the already existing peptides Exendin-4 & ED11. Moreover, novel peptides NP_1, NP_3 & NP_6 showed much lower total energy values -2313.71 kcal/mol, -2247.98 kcal/mol and -2240.76 kcal/mol respectively. Among these, NP_1 has the lowest total energy value and also found to interact at active site pocket as shown in Figure 5.

NP_1 was found to be the best designed peptide for further analysis. Hence, its structure was drawn and NMR analysis was performed by prediction software as shown in Figure 6. The ball and structure design of NP_1 was also analyzed.

The analysis of 29 amino acids NP1 structure summarized that the molecular weight is 3310.6 and the net charge is 0. The isoelectric point is 7. Altogether the structure of NP1 is stable and docking of protein peptide is convincing. NP_1 is also nontoxic as predicted by ToxinPred. Hence it has been selected as the best peptide for future analysis. However, NP_5 and NP_6 may also be checked for future analysis as they demonstrate no amyloidic region for aggregation.

4. Discussion

4.1. Huntingtin interacting protein and intervention of peptide for Huntington's therapy

The wild-type Htt protein is known to interact with almost 19 other proteins. Some of the interacting proteins are BDNF, Grb2, HIP, HAP, HDAC, Ras and transcription factors like p53, Sp1, SIN3a, NF-kB in Figure 7 [42]. The interaction ability of wild-type Htt gets affected in mutant Htt, which is unknown till now but the interaction might be

Table 4. The summary of above-mentioned novel peptides based on minimum values of the energies.

S.No.	Peptide Name	Model No.	E receptor (kcal/mol)	E ligand (kcal/mol)	E interaction (kcal/mol)	E total (kcal/mol)
1	**NP_1**	**8**	**-2175.12**	**-138.59**	**0**	**-2313.71**
2	NP_2	8	-1980.15	-124.93	0	-2105.08
3	**NP_3**	**3**	**-2043.83**	**-192.75**	**-11.4**	**-2247.98**
4	NP_4	10	-2009.68	-93.47	0	-2103.15
5	NP_5	10	-2054.55	-97.68	0	-2152.23
6	**NP_6**	**5**	**-2102.08**	**-77.88**	**-60.8**	**-2240.76**

Note: The minimum negative energies have been highlighted in bold.

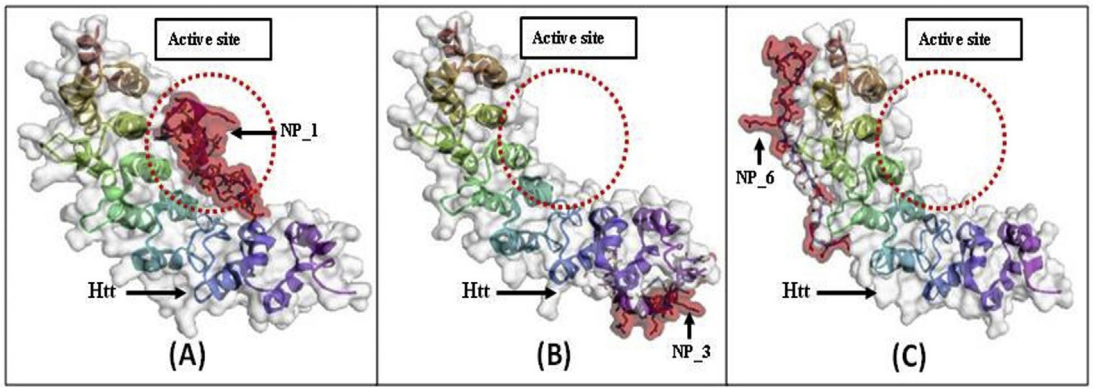

Figure 5. The figure shows docked structures of (A) NP_1, (B) NP_3, (C) NP_6, with Htt model. Note: The dotted circle indicates the active site.

affected in mutated condition worsening the symptoms of HD. The designed peptide NP_1 might be able to reduce the severity of the disease.

Htt protein with expanded polyglutamine repeat is called mutated Htt (mHtt)protein, which makes mHtt highly unstable and aggregation prone. Mutant Htt aggregates drive progression of Huntington's disease. Amongst the proteins that interact with Htt are HDAC3, Hsp90 [43], HIP (Huntingtin interacting protein), HAP (Huntingtin associated protein) CREBBP, BDNF, caspase [44, 45, 46] etc. Mutated Htt is unable to interact with HDAC3 and performs the cellular process which contributes in neurodegeneration [47, 48]. Huntingtin is known to upregulate BDNF by unknown transcriptional mechanism. Mutant Htt interferes with membrane flipodial dynamics unlike its wild type.

Several peptides are able to prevent this neurodegeneration, and these peptides are QBP1, p42, ED11, Exendin 4 etc. (QBP1) 2, ED11, CaM and p42 peptide has established therapeutic value in Huntington's disease by targeting mutant Htt and preventing its interaction with other proteins. CaM peptide is known to prevent the interaction between mutant Htt and CaM and thereby play its therapeutic role. ED11 targets caspase 6 for its therapeutic efficacy. On contrary, Exendin 4 peptide has wide therapeutic value like diabetes, cancer, cardiovascular disorder and

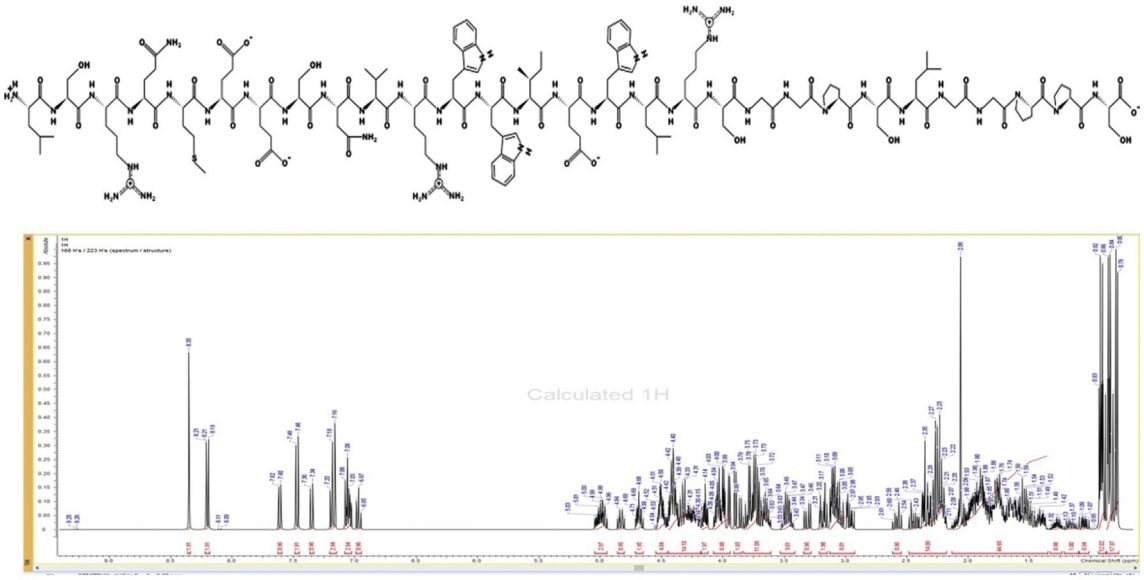

Figure 6. NP1 structure, "LSRQMEESNVRWWIEWLRSGGPSLGGPPS" prediction through NMR and ball and structure design shown (Courtesy: ACD Labs Canada (1H NMR Predictors, version 2019.1, Advanced Chemistry Development, Inc., Toronto, On, Canada, www.acdlabs.com, 2019) for predicting the NMR structure of NP1 Peptide. S.

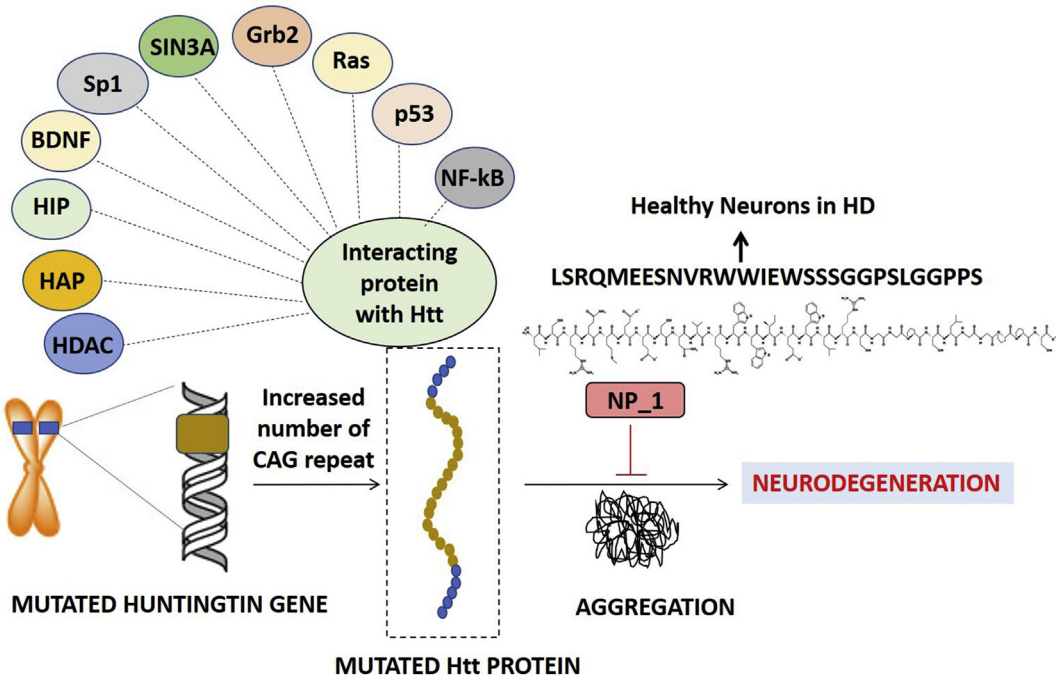

Figure 7. Role of designed peptide NP_1 in huntingtin interactome with its interacting protein.

Huntington's disease. Hence this peptide has been included for comparison and designing purpose in this article. Amongst the designed peptide NP_1 is selected as the best designed peptide due to its docking efficacy with Htt and non-toxicity predicted by ToxinPred analysis.

Current research has identified till date nine types of PolyQ disorders including dentatorubralpallidoluysian atrophy (DRPLA), Huntington's disease (HD), spinal-bulbar muscular atrophy (SBMA), and six spinocerebellar ataxias (SCA 1, 2, 3, 6, 7, and 17). Amongst them, the rarest disorder is Huntington's disease which is an adult-onset progressive neurodegenerative polyglutamine disorder caused by an expansion of CAG triplet repeats within the coding region of Htt gene. Normally, Htt gene has 35–36 glutamine repeats while the diseased state show increase in the number of repeats. It has been observed that the mortality rates caused by HD are very high. Due to these increasing mortality rates, it becomes a necessity to discover new and efficient therapeutic approaches for preventing these diseases to occur. Previously, various approaches including ubiquitin-proteasomal system, RNA silencing, HSP 70/HSP90 models have been developed to treat HD and but none of them showed promising results. Here, the therapeutic approach used for ameliorating HD is "Peptide-based therapy". With this approach, novel peptides are designed that have the potential to prevent the progression of disease.

5. Conclusion

Our study suggest that the designed peptide binds to the active site of Htt protein thus preventing the degeneration of neuronal cells caused by HD. According to our study, the three novel peptides-NP_1, NP_3 and NP_6 depicted better total energy values than the chosen test peptides ED 11 and Exendin-4. The energy values for NP_1, NP_3, NP_6 are -2313.71 kcal/mol, -2247.98 kcal/mol and -2240.76 kcal/mol respectively whereas of ED11 and Exendin-4 are 2184.63 kcal/mol and -2129.88 kcal/mol respectively. Since, NP_1 showed significant difference in total energy along with the binding at the active pocket of Htt protein, it can have a potential role in ameliorating HD symptoms and can also be used in further research for treating other PolyQ disorders. Therefore, NP_1, NP_5 and NP_6 may be studied for future analysis based on docking and aggregation ability.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

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