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Peptide Based Vaccine against Human Herpes Virus-7 Using in Silico Approach

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Abstract: ***Background: Human Herpesvirus 7 (HHV-7) appears to be principally acquired in infancy and childhood and able to cause roseola. No such vaccine is available that can cure the virus with cross-protection. Thus this study involves a peptide based vaccine design with the help of immunoinformatics approach. Objectives: To design a peptide based vaccine for herpes virus-7 using immune informatics tools. Materials and Methods: sequences of envelope glycoprotein H were retrieved from National Center of Biotechnology Information (NCBI) database in 2020 and aligned to determine the conservancy between the retrieved strains. The Immune Epitope Data Base (IEDB) different analysis resources were used to predict epitopes that could act as a peptide vaccine against herpes virus 7. The predicted epitopes were further assessed for population coverage against the whole world population. Results: The epitopes 81-FDQYKHR$_{87}$, $_{141}$IRKLYYNQ$_{148}$, $_{478}$KDLTQRVV$_{485}$, $_{342}$LLYPEMEKL$_{350}$, 572-CTPTNYKYS 580, 97-EKAVKIYAQ 105, 106-KFQTNIKPV 114 and 506-SVYRKKRLDM 515 were found to be the most potential eight epitopes against B cells. For the T cell Three epitopes namely, $_{180}$FMLALTPSF$_{188}$, $_{238}$TTIERFYPF$_{246}$ and $_{616}$YIMDDKQLL$_{624}$ showed high affinity to MHC-I alleles , The Three epitopes (core) $_{347}$MEKLQNFQL$_{355}$, $_{50}$YNETRVYQI$_{58}$ and $_{512}$RLDMFKSIS$_{520}$ showed high affinity to interact with MHC-II alleles, high coverage for whole world population with percentage of 80.70% and 61.02% respectively. Conclusions: This study proposed eight epitopes for B and six for T cells that could be a powerful multi epitope vaccine, Clinical trial like experimental animals is required to proof the efficacy of these epitopes as promising candidate vaccine against human herpes 7.***

Keywords: Peptide Based Vaccine, Human Herpes Virus-7, Insilico Approach

1. Introduction

Herpes virus family is a group of viruses that can infect both animals and humans. Over 130 species of herpes virus are known, but only eight of these are known to infect humans, Varicella zoster virus, Cytomegalovirus, Epstein-Barr virus, Herpes simplex virus 1, Herpes simplex virus 2, Kaposi sarcoma –associated herpes virus, B virus, and herpes virus 7. These, collectively, are known as human herpes virus, or HHV which are belong to DNA viruses [(1)]

Human herpes beta viruses are contagious, which means that they are passed from person to person. Because they do not live for long outside the human body, they are usually passed on by direct contact with bodily fluids, rather than infected objects) [(2)]

Human herpes virus-7 is a ubiquitous virus that belongs to the subfamily of β-herpesviruses (together with cytomegalovirus and human herpesvirus-6). Primary infection usually occurs during childhood and may cause several clinical manifestations: mainly exanthem subitum (*roseola infantum*), followed by a lifelong latent state with possible reactivation in case of immunodeficiency) [(1),] affects upwards of 90 % of all adults worldwide. Infection usually occurs in childhood or infancy [(3)] and is usually asymptomatic. The conditions caused by this human herpesvirus are generally less well-understood overall than those caused by some of the other strains of the virus.

In children, primary infection can cause a fever, on its own or in combination with other symptoms in a condition that resembles roseola infantum. While Human Herpes Virus 7 is less likely to reactivate than some other human herpes viruses, it can reactivate in people with weakened immune systems, especially among people who have recently received organ transplants. Infections caused by Human Herpes Virus 7 are not generally very serious in people with healthy immune systems [(4)]

Peptide base vaccines are built of defined small peptide antigens engineered to induce the desired immune response, peptide vaccines reduce cost, reducing risks of allergic and autoimmune responses ([5, 6)] In this study immune informatics approach was used to design peptides base vaccine against Herpes virus 7.

2. Materials and Methods

The reference sequence of envelope glycoprotein H was reported as most immunogenic part for the Herpes virus 7 [7]

The reference sequence and other amino acid sequences of glycoprotein H herpes virus 7 were retrieved in FASTA format from the protein sequence database of National Center for Biotechnology Information NCBI. (http://www.ncbi.nlm.nih.gov/protein). Sequences accession numbers; year and country of isolation were shown in Table1.

Table 1: The Retrieved Strains, Accession Numbers and Area of Collection:

NO	Accession	Area	Year
1*	YP_073788	USA	13-AUG-2018
2	AAB64293	USA	19-JAN-2001
3	AAK26658	Thailand	25-JUN-2002
4	AAC54710	USA	29-MAR-1996
5	AAK26657	Thailand	25-JUN-2002
6	AAK26656	Thailand	25-JUN-2002
7	AAK26655	Thailand	25-JUN-2002
8	AAK26654	Thailand	25-JUN-2002
9	AAK26653	Thailand	25-JUN-2002
10	AAK26652	Thailand	25-JUN-2002

3. Results

Figure 1 showed Phylogenetic Evolution tree of all Retrieved Strains done by using glycoprotein H OF Herpes virus 7

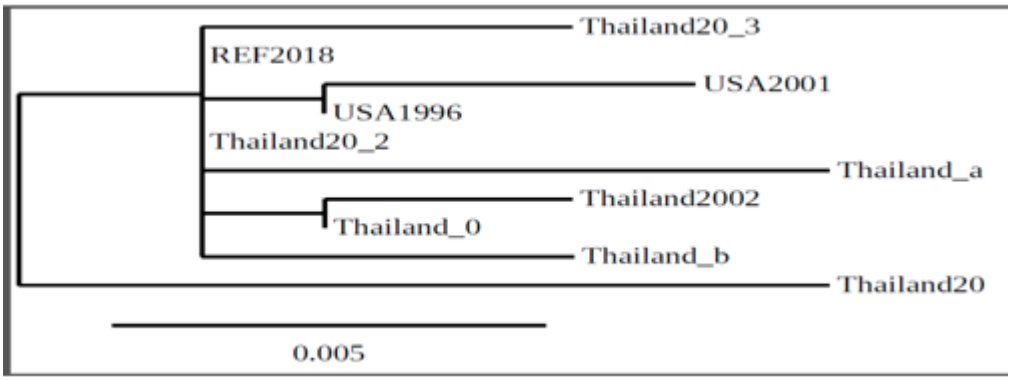

Figure 1: Cladogram Showed the Relationship between the different Herpes virus 7 glycoprotein H Strains

Figure 2 showed that some alignment regions were mutated region, and dots show the conservancy between different retrieved sequences.

Figure 2: Multiple Sequence Alignment of Retrieved Strains

Prediction of B-cell Epitopes:

The reference sequence of beta herpes virus 7 gH was subjected to Bepipred linear epitope, Emini surface accessibility and Kolaskar and Tongaonkar antigenicity methods in IEDB to predict the likelihood of specific regions in the protein that bind to B cell receptor, being in the surface and immunogenic respectively. For Bepipredlinear epitope prediction method, the average binding score of viral protein to B cell was 0.5. Thirty four (34) epitopes were predicted as a linear epitopes and only (25) epitopes were conserved regions. Emini surface accessibility provided only 15 epitopes that were potentially predicted on surface by passing the default threshold 1.000. Kolaskar and Tongaonkar antigenicity provided 21 epitopes that gave score above the default

threshold 1.021. Allergencity provided only 14 epitopes that gave non allergen and toxin pred showed all 25 epitopes were non toxin. The epitopes 81-FDQYKHR-87, 141-IRKLYYNQ-148, 478-KDLTQRVV-485, 342-LLYPEMEKL-350, 572-CTPTNYKYS-580, 97-EKAVKIYAQ-105, 106-KFQTNIKPV-114 and 506-SVYRKKRLDM-515. was predicted by these different tools against B cell as provided in Table 1.

T lymphocytes Epitopes Binding Prediction

MHC-I Binding Predictions:

The reference structural gH was analyzed using IEDB MHC-1 binding prediction tool to predict T cell epitopes interacting with different types of MHC-I alleles.129 conserved epitopes were predicted to interact with different MHC-1 alleles. The peptides, 180-**FMLALTPSF**-188 had higher affinity to interact with 8 alleles, also 238-**TTIERFYPF**-246 that interacted with 7 alleles and 616-**YIMDDKQLL**-624. that interacted with 6 alleles as shown in Table 4.2. These three epitopes and their positions in structural level of glycoprotein H were shown in **Figure 4**.

The 129 conserved peptides and their interaction with different MHC-1 alleles were supplemented in an extra sheet 1

Table 1: B-cell epitopes prediction, the position of peptides is according to the position of amino acids in the glycoprotein H of herpes virus 7.

No.	Start	End	Peptide	Length	Conserve	Emini 1.000	Antigenicity 1.047	Allergenicity	Toxigenicity
1	352	355	NFQL	4	C	0.797	1.033	PROBABLE ALLERGEN	Non-Toxin
2	308	312	GDGLL	5	C	0.356	1.023	PROBABLE ALLERGEN	Non-Toxin
3	282	287	CGKPVN	6	C	0.502	1.073	PROBABLE ALLERGEN	Non-Toxin
4	429	434	LVFQEK	6	C	0.815	1.087	PROBABLE NON-ALLERGEN	Non-Toxin
5	336	341	KMTKSH	6	C	2.671	0.952	PROBABLE NON-ALLERGEN	Non-Toxin
6	17	23	WKHWNIL	7	C	0.577	1	PROBABLE NON-ALLERGEN	Non-Toxin
7	459	465	LDNVMDI	7	C	0.393	1.017	PROBABLE ALLERGEN	Non-Toxin
8	657	663	LDLKSSQ	7	C	1.457	1.048	PROBABLE ALLERGEN	Non-Toxin
9	81	87	FDQYKHR	7	C	4.312	1.006	PROBABLE NON-ALLERGEN	Non-Toxin
10	141	148	IRKLYYNQ	8	C	2.59	1.04	PROBABLE NON-ALLERGEN	Non-Toxin
11	73	80	DSVNFDES	8	C	1.5	0.982	PROBABLE ALLERGEN	Non-Toxin
12	209	216	RIFFKAPF	8	C	0.466	1.044	PROBABLE NON-ALLERGEN	Non-Toxin
13	478	485	KDLTQRVV	8	C	1.242	1.076	PROBABLE NON-ALLERGEN	Non-Toxin
14	342	350	LLYPEMEKL	9	C	1.097	1.048	PROBABLE NON-ALLERGEN	Non-Toxin
15	572	580	CTPTNYKYS	9	C	2.483	1.037	PROBABLE NON-ALLERGEN	Non-Toxin
16	581	589	VKNIKPIYN	9	C	1.242	1.036	PROBABLE ALLERGEN	Non-Toxin
17	97	105	EKAVKIYAQ	9	C	1.357	1.061	PROBABLE NON-ALLERGEN	Non-Toxin
18	106	114	KFQTNIKPV	9	C	1.522	1.028	PROBABLE NON-ALLERGEN	Non-Toxin
19	115	123	SHTKTITVS	9	C	1.039	1.036	PROBABLE ALLERGEN	Non-Toxin
20	405	414	HKLFTNLTQP	10	C	1.579	1.03	PROBABLE ALLERGEN	Non-Toxin
21	506	515	SVYRKKRLDM	10	C	3.579	1.01	PROBABLE NON-ALLERGEN	Non-Toxin
22	27	37	ICVNEKTNQTI	11	C	0.564	1.024	PROBABLE NON-ALLERGEN	Non-Toxin
23	240	252	IERFYPFLKIDFL	13	C	0.347	1.063	PROBABLE NON-ALLERGEN	Non-Toxin
24	486	500	NNILSYKNLDAYTNK	15	C	3.799	0.986	PROBABLE ALLERGEN	Non-Toxin

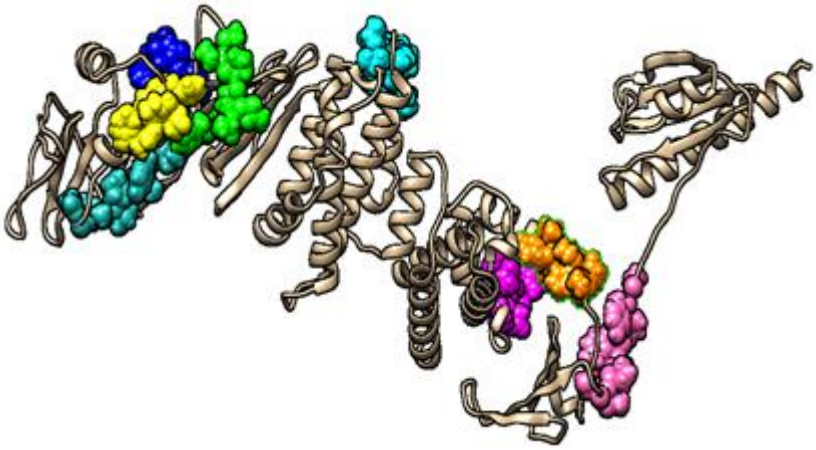

Figure 3: Position of Proposed Conserved B Cell Epitope in Structural Level of glycoprotein H of herpes virus 7

Table 2: List of Top Epitopes that had Binding Affinity with MHC-I alleles. The position of peptides is according to position of amino acids in glycoprotein H of Herpes virus 7.

Peptide	Start	End	Allele	ic50
FMLALTPSF	180	188	HLA-A*02: 01 HLA-A*02: 06 HLA-A*29: 02 HLA-A*32: 01 HLA-B*15: 01 HLA-B*15: 02 HLA-B*35: 01 HLA-C*14: 02	26.95 9.41 53.84 48.72 14.24 33.64 14.93 13.59
TTIERFYPF	238	246	HLA-A*02: 06 HLA-A*23: 01 HLA-A*26: 01 HLA-A*32: 01 HLA-A*68: 02 HLA-B*08: 01 HLA-B*15: 01	10.82 45.95 15.71 13.87 35.79 96.89 30.03
YIMDDKQLL	616	624	HLA-A*02: 01 HLA-A*02: 06 HLA-C*03: 03 HLA-C*07: 01 HLA-C*12: 03 HLA-C*14: 02	36.3 33.66 44.04 64.55 99.2 78.61

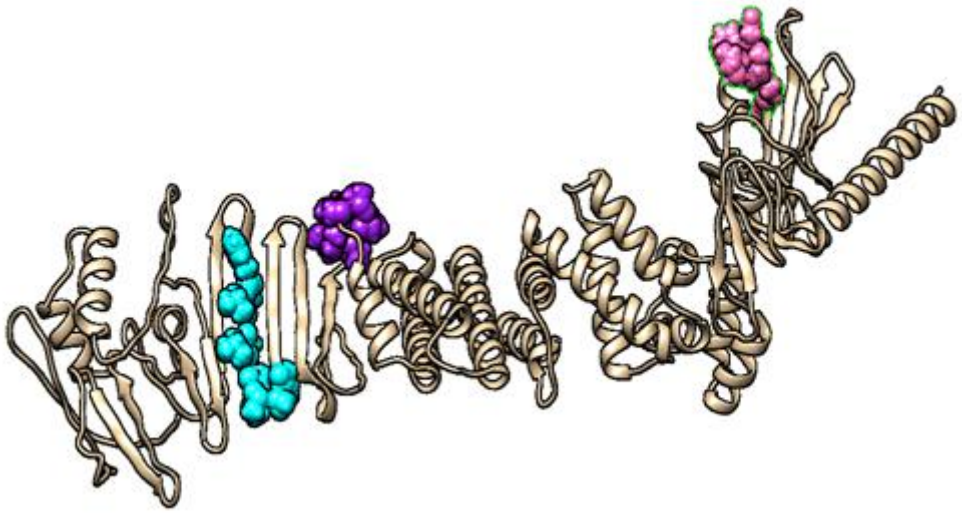

Figure 4: Position of Proposed Conserved T Cell Epitopes that Interact with MHC-I in Structural level of glycoprotein H herpes Virus 7

MHC-II Binding Predictions:

A three hundred sixty eight (368) conserved epitopes were predicted from reference glycoprotein H which has ability to interact with MHC-II alleles. As shown in Table 4.3 three epitopes (core) $_{347}$-**MEKLQNFQL**-$_{355}$, $_{50}$-**YNETRVYQI**-$_{58}$ **,** and $_{512}$-**RLDMFKSIS**-$_{520}$ demonstrated higher affinity to interact with MHC-II alleles. The three dimensional structural level (3D) of these epitopes within glycoprotein H was shown in Figure 4.5. The other core epitopes and their corresponding alleles that interacted with MHC-II were supplemented in an extra sheet-2.

Core Sequence	Peptide Sequence	Start	End	Allele	IC50
MEKLQNFQL	YPEMEKLQNFQLVDY	344	358	HLA-DRB1*01: 01	18.4
	PEMEKLQNFQLVDYS	345	359	HLA-DRB1*01: 01	22.2
	LYPEMEKLQNFQLVD	343	357	HLA-DRB1*01: 01	26.7
	EMEKLQNFQLVDYSY	346	360	HLA-DRB1*01: 01	28.1
	MEKLQNFQLVDYSYI	347	361	HLA-DRB1*01: 01	33.6
	LLYPEMEKLQNFQLV	342	356	HLA-DRB1*01: 01	34
	HLLYPEMEKLQNFQL	341	355	HLA-DRB1*01: 01	138.7
	YPEMEKLQNFQLVDY	344	358	HLA-DRB1*10: 01	66.5
	EMEKLQNFQLVDYSY	346	360	HLA-DRB1*10: 01	70
	LYPEMEKLQNFQLVD	343	357	HLA-DRB1*10: 01	70.9
	PEMEKLQNFQLVDYS	345	359	HLA-DRB1*10: 01	85.2
	LLYPEMEKLQNFQLV	342	356	HLA-DRB1*10: 01	88.8
	HLLYPEMEKLQNFQL	341	355	HLA-DRB1*10: 01	125.4
	LYPEMEKLQNFQLVD	343	357	HLA-DRB1*12: 01	297.1
	YPEMEKLQNFQLVDY	344	358	HLA-DRB1*15: 01	186.3
	PEMEKLQNFQLVDYS	345	359	HLA-DRB1*15: 01	195.2
	EMEKLQNFQLVDYSY	346	360	HLA-DRB1*15: 01	206.7
	LYPEMEKLQNFQLVD	343	357	HLA-DRB1*15: 01	268.3
	MEKLQNFQLVDYSYI	347	361	HLA-DRB1*15: 01	270.2
	YPEMEKLQNFQLVDY	344	358	HLA-DRB1*16: 02	227.9
	PEMEKLQNFQLVDYS	345	359	HLA-DRB1*16: 02	231.8
	EMEKLQNFQLVDYSY	346	360	HLA-DRB1*16: 02	264.5
	LYPEMEKLQNFQLVD	343	357	HLA-DRB1*16: 02	276.6
YNETRVYQI	TFNFHDYNETRVYQI	44	58	HLA-DRB1*07: 01	19
	FNFHDYNETRVYQIP	45	59	HLA-DRB1*07: 01	23
	NFHDYNETRVYQIPK	46	60	HLA-DRB1*07: 01	28.6
	FHDYNETRVYQIPKC	47	61	HLA-DRB1*07: 01	41.4
	HDYNETRVYQIPKCL	48	62	HLA-DRB1*07: 01	59.6
	DYNETRVYQIPKCLF	49	63	HLA-DRB1*07: 01	67.4
	YNETRVYQIPKCLFG	50	64	HLA-DRB1*07: 01	150.6
RLDMFKSIS	KKRLDMFKSISCVSN	510	524	HLA-DRB1*04: 04	81.4
	KRLDMFKSISCVSNE	511	525	HLA-DRB1*04: 04	82.6
	RKKRLDMFKSISCVS	509	523	HLA-DRB1*04: 04	102.1
	YRKKRLDMFKSISCV	508	522	HLA-DRB1*04: 04	134.7
	VYRKKRLDMFKSISC	507	521	HLA-DRB1*04: 04	151.6
	SVYRKKRLDMFKSIS	506	520	HLA-DRB1*04: 04	228.8
	KKRLDMFKSISCVSN	510	524	HLA-DRB1*11: 01	88.8
	RKKRLDMFKSISCVS	509	523	HLA-DRB1*11: 01	104.6
	YRKKRLDMFKSISCV	508	522	HLA-DRB1*16: 02	54
	VYRKKRLDMFKSISC	507	521	HLA-DRB1*16: 02	76.4
	SVYRKKRLDMFKSIS	506	520	HLA-DRB1*16: 02	139.1

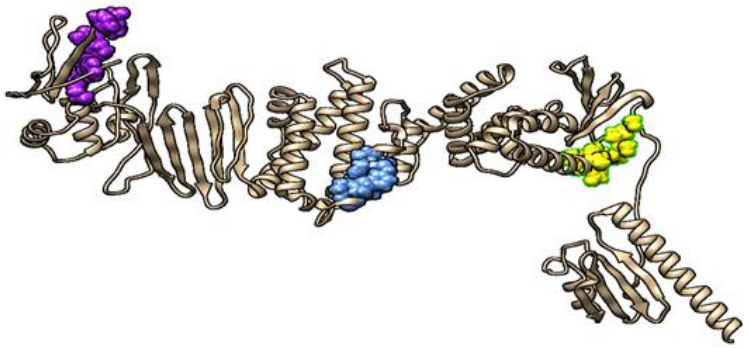

Figure 5: Position of proposed conserved T cell epitopes that interact with MHC-II of glycoprotein herprs Virus 7.

Population Coverage

Population coverage was performed for predicted T-cell epitopes and their respective MHC-I and MHC-II alleles. As shown in Table 4.4 the selected three epitopes that interacted with most frequent MHC-I alleles $_{180}$-**FMLALTPSF**$_{-188,}$ $_{238}$-**TTIERFYPF**$_{-246}$ and $_{616}$-**YIMDDKQLL**$_{-624.}$ demonstrated population coverage against the whole world 80.70% Three epitopes $_{347}$-**MEKLQNFQL**$_{-355}$, $_{50}$-**YNETRVYQI**$_{-58}$, and $_{512}$-**RLDMFKSIS**$_{-520}$ demonstrated population coverage against the whole world 61.02% against MHC-II. The overall epitope sets for the predicted epitopes against MHC-I alleles and MHC-II alleles was 84.43% as shown in Table 4.4 and 4.5.

Table 4: The Population Coverage against the Whole World for the Predicted epitopes

Epitope	Coverage Class I	Total HLA hits	Epitope	Coverage Class II	Total HLA hits
FMLALTPSF	58.27%	8	MEKLQNFQL	36.26%	5
TTIERFYPF	34.41%	7	YNETRVYQI	18.23%	1
YIMDDKQLL	63.14%	6	RLDMFKSIS	16.85%	3
Epitope Set	80.70%	21	Epitope Set	61.02%	9

Table 5: The Population Coverage against the Whole World for the Predicted Epitopes against both MHC-1 and MHC-11

Epitope	Coverage Class I&II	Total HLA hits
FMLALTPSF	58.27%	8
TTIERFYPF	34.41%	7
YIMDDKQLL	63.14%	6
MEKLQNFQL	36.26%	5
YNETRVYQI	18.23%	1
RLDMFKSIS	16.85%	3
Epitope set	92.48%	30

4. Discussion

Human herpes virus 7 have recently been isolated. HHV 7 has been associated with exanthem subitum, or roseola. This illness is characterized by 3 – 5 days of fever, followed by the appearance of a macula papular "slapped cheek" rash. In addition, there has been an association between human herpes virus 7 and rejection of transplanted kidneys, fulminate hepatitis and infections of the central nervous system [8]

Designing epitope-based peptide vaccine has the growing interest for the viral vaccination due to the recent advances in protein data and sequencing technologies. Additionally, it allows the immune response to focus solely on relevant epitopes, avoiding those that lead to non-protective responses, immune evasion, or unwanted side effects.

This study aimed to determine a 100% conserved regions which are then investigated to predict the highly potential immunogenic epitopes for both B and T cells using glycoprotein H of herpes virus 7, glycoprotein H has been proposed by P Secchiero et al as a good candidate protein for vaccine against herpes 7 virus [9] Our results revealed eight promising epitopes for B cell 81-FDQYKHR$_{-87,}$ $_{141}$-IRKLYYNQ$_{-148}$, $_{478}$-KDLTQRVV$_{-485}$, $_{342}$-LLYPEMEKL$_{-350,}$ 572-CTPTNYKYS.580, 97-EKAVKIYAQ.105, 106-KFQTNIKPV.114 and 506-SVYRKKRLDM.515. this epitopes had a higher predicted score for surface accessibility and antigenicity, moreover this epitopes showed non toxic and non-allergic effect. This epitopes probably activating humeral immune response as it is part of glycoprotein H [10]

In prediction of T-cell the epitopes interacting with different types of MHC-I alleles.129 conserved epitopes were predicted to interact with different MHC-1 alleles. The epitopes $_{180}$-**FMLALTPSF**$_{-188}$ had higher affinity to interact with eight alleles, also,, $_{238}$-**TTIERFYPF**$_{-246}$ that interacted with seven alleles while the epitope $_{616}$-**YIMDDKQLL**$_{-624}$ that interacted with six alleles.

Our prediction of these epitopes to binding with different alleles agreed with concept of Vikas Sharma, [1] Fauzul Mobeen, [1] and Tulika Prakas.

A three hundred sixty eight (368) conserved epitopes were predicted from reference glycoprotein H which has ability to interact with MHC-II alleles. The (core) $_{347}$-**MEKLQNFQL**$_{-355}$ interact with 5 HLA the core $_{50}$-**YNETRVYQI**$_{-58}$ interact with one allele and the core $_{512}$-**RLDMFKSIS**$_{-520}$ interact with 3 HLA [11]

Vikas Sharma, [1] Fauzul Mobeen, [1] and Tulika Prakas identified only three epitopes in the genome of Human Herpes Virus 7 which are present on the antigenic proteins [12]

5. Conclusions

This study predict the following epitopes to be used as herpes virus 7 vaccine: The epitopes 81-FDQYKHR$_{-87,}$ $_{141}$-IRKLYYNQ$_{-148}$, $_{478}$-KDLTQRVV$_{-485}$, $_{342}$-LLYPEMEKL$_{-350,}$ 572-CTPTNYKYS.580, 97-EKAVKIYAQ.105, 106-KFQTNIKPV.114 and 506-SVYRKKRLDM.515 were predicted against B cell. The peptides$_{180}$-**FMLALTPSF**$_{-188,}$ $_{238}$-**TTIERFYPF**$_{-246}$ and $_{616}$-**YIMDDKQLL**$_{-624.}$ were predicted against MHC I. three epitopes (core) $_{347}$-**MEKLQNFQL**$_{-355}$, $_{50}$-**YNETRVYQI**$_{-58}$, and $_{512}$-**RLDMFKSIS**$_{-520}$ were predicted against MHCII. Further

in vitro and in vivo studies could to determine the actual potency of identified epitopes to stimulate immune response.

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