Molecular Docking of Some Peptides to Varicella Zoster Virus Drug Targets

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الخلاصة

يعد فيروس الحماق النطاقي (جدري الماء)، فيروس الهربس الموجه للعصب، هو العامل المسبب لكلاً من الحماق (جدري الماء) والنطاقي (القوباء المنطقية). كما هو الحال مع فيروسات الهربس الاخرى، جدري الماء يسبب كلا الأمراض الحادة والامراض الكامنة مدى الحياة. وان فيروس النطاقي الحماقي هو فايروس شائع خلال مرحلة الطفولة وخاصة في المناخات المعتدلة. الحماق عادة هو مرض حميد ويشفى من تلقاء نفسه، ولكن يمكن أن يكون أكثر شدة عند البالغين والأشخاص ذوي المناعة القليلة. وان الهدف من هذه الدراسة هو التنبؤ او انتخاب أفضل الببتيدات بطريقة حاسوبية لكي يتم اثباتها تجريبيا عن طريق المختبر وتوضيح قدرتها في معالجة فايروس النطاقي الحماقي. في هذه الدراسة تم استخدام العديد من الببتيدات المضادة للميكروبات والببتيدات المضادة للفيروسات لتوقع فعالية هذه الببتيدات ضد ثلاثة أهداف من فيروس النطاقي الحماقي وهذه الاهداف تشمل Thymidine kinase (PDBID: 1OSN), Envelope glycoprotein H (PDBID:4XHJ), Protease (PDBID: 1VZV)) باستخدام نهج المعلوماتية الحيوية.

ومن ثم تم التنبؤ بقابلية ارتباط الببتيدات مع الاهداف الفيروسية باستخدام برنامج (Hex 8.0.0)على شبكة الإنترنت. بالإضافة إلى ذلك تم حساب بعض الخصائص الفيزيائية والكيميائية للببتيدات بواسطة عدة برامج محددة بها في ذلك: T cell epitope Class I immunogenicity (ToxinPred, CellPPD hydropathicit، نقطة التعادل الكهربائي PI والوزن الجزيئي، Boman index values وبرنامج anti-cp . ومن مجموع 64 ببتيد مضاد للميكروبات التي تم جمعها من عدة أبحاث ظهر ان فقد تم اختيار 11 ببتيد وذلك لامتلاكهم

شدة ارتباط جيدة مع أهداف الفيروس النطاقي الحماقي وكانت الخصائص الفيزيائية والكيميائية لهذه الببتيدات جيدة. وتشمل هذه الببتيدات: (16-Polyphemusin 2، K4S4 (1 ، F، AVP 1092، MSI-78، 1074 AVP 5.6، Dahlein 1، Magainin GLK-19، Fv16، A. وأخيرا، هناك حاجة للمزيد من التجارب المختبرية لكي يثبت ان هذه الببتيدات المضادة للفايروس يمكن ان تستخدم كدواء مضاد لفيروس الحماق النطاقي.

الكلمات المفتاحية

الحماق النطاقي، فيروس الهربس، الببتيدات.

Abstract

Varicella-zoster virus (VZV), a neurotropic herpesvirus, is the causative agent of both varicella (chickenpox) and zoster (shingles). Like another herpes viruses, the VZV can cause both acute illness and latency lifelong. In other hand, the VZV common during childhood, especially in temperate climates. Moreover, Varicella is usually a benign and self-limiting illness. But may be more severe in adults, and in patients suffering from immunedeficiency. Because of the huge information available concerning inhibitors of this virus the current study spots light on them bypredicting the best peptides that can be a candidate to offer to wet laboratory experiments sufficient data about their ability to treat VZV. To acheve this aim several antimicrobial peptides and antiviral peptides used to predict their theoretical actions against three targets of VZV, Thymidine kinase (PDBID: 1OSN), Envelope glycoprotein H (PDBID: 4XHJ), Protease (PDBID: 1VZV) using Bioinformatics approach. And the binding potential of these peptides with the VZV drug targets was predicted using online program Hex 8.0.0., and some physical and chemical properites of peptides were predicted by specific programs, including T cell epitope Class I immunogenicity software, ToxinPred software, CellPPD software, isoelectric points (PI) and molecular weight, Boman index values software, and anti-cp software. The analysis of these data resulted with that from 64 antimicrobial peptide only 11 peptides have been found have favored binding affinities with VZV targets and good physical and chemical properties, these peptides were Polyphemusin 2, K4S4(1-16) a, F, AVP1092, MSI-78, A, Fv16, GLK-19, Magainin 1, Dahlen 5.6.

Keywords

Varicella, zoster, peptides.

1. Introduction

Varicella zoster virus (VZV) is an exclusively human virus that belongs to the α-herpes virus family. The VZV present worldwide and is highly infectious. Moreover, the primary infection leads to acute varicella or "chickenpox", usually from exposure either through direct contact with a skin lesion or through airborne spread from respiratory droplets [1, 2]. In addition, more than 90% of adults in the United States acquired the disease in childhood, while the majority of children and young adults have been vaccinated with the live virus vaccine [3]. The increasing incidence of VZV in patient aged 15 years or has resulted in an increase in severe forms and in mortality, also cases of resistance to classical antiviral treatment. Unusual forms of varicella and zoster are occasionally encountered even in non-immune compromised patients. Infections of VZV are a matter of concern in high-risk groups includes immune compromised children and adults [4].

The aim of this current study is to predict the best antimicrobial peptides (AMP) that can be a candidate to offer these peptides to the laboratory experiments, to show their ability to inhibit VZV. Consequently, this aim was done by picking about 64 short peptides by gathering these sequences from the web server, and entered them in specific computer programs to know their strength for binding to receptors of VZV by molecular docking, in addition calculating the probability of cell penetrating, physicochemical properties and other parameters.

Materials and Methods

2. Materials

2.1. Short Peptides

Sixty-four short peptides sequences used to predict their anti-VZV attachment and to study their physical and chemical properties. These peptides listed below in Table 1.

Table (1): Short peptides used in current study with their sequences

No	Peptide	Sequence	Reference
9	Brevinin-1BYa	FLPILASLAAKFGPKLFCLVTKKC	[10]
10	Brevinin-1BYb	FLPILASLAAKLGPKLFCLVTKKC	[10]
11	Brevinin-1BYc	FLPILASLAATLGPKLLCLITKKC	[10]
1	A	VVKKARKAAKKVAKK	[5]
2	Alloferon 1	HGVSGHGQHGVHG	[6]
3	Alloferon 2	GVSGHGQHGVHG	[6]
4	Androctonin	RSVCRQIKICRRRGGCYYKCTNRPY	[7]
13	C	TGKIGKLKKGTGKIA	[71]
16	D	AIRRLARRGGVKRISGLI	[71]
22	FV16	KKVGTSKVVAKTVTKK	[71]
54	F	KATKATITKKPVA	[71]
37	polyphemusin II	RRWCFRVCYKGFCYRKCR	[73]
38	Protegrin PG-1	RGGRLCYCRRRFCVCVGR	[73]

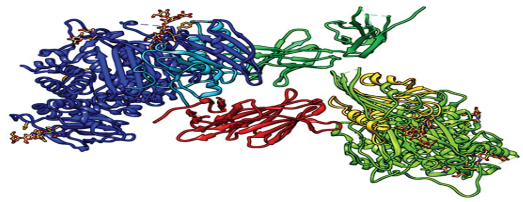
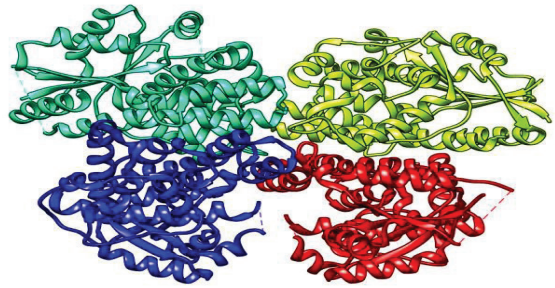
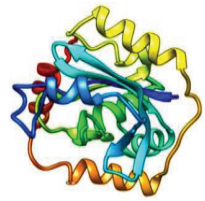
43	Tachyplesin I	KWCFRVCYRGICYRRCR	[73]
48	Citropin 1.1	GLFDVIKKVASVIGGL	[74]
14	CP11	ILKKWPWWPWRRK	[11]
15	Cp10A	ILAWKWAWWAWRR	[11]
26	Indolicidin	ILPWKWPWWPWRR	[11]
17	DET1	GWVKPAKLDG	[12]
18	DET2	PWLKPGDLDL	[12]
19	DET3	IGVRPGKLDL	[12]
20	DET4	AGVKDGKLDF	[12]
21	Dahlein 5.6	GLLASLGKVFGGYLAEKLKPK	[13]
32	Maculatin 1.1	GLFGVLAKVAAHVVPAIAEHF	[13]
40	Ranatuerin-6	FISAIASMLGKFL	[13]
44	Uperin 3.6	GVIDAAKKWNVLKNLF	[13]
45	Caerin 1.1	GLLSVLGSVAKHVLPHVVPVIAEHL	[13]
46	Caerin 1.9	GLFGVLGSIAKHVLPHVVPVIAEKL	[13]
47	Caerin 4.1	GLWQKIKSAAGDLASGIVEGIKS	[13]
5	Aurein 1.2	GLFDIIKKIAESF	[8]
23	HNP-1ΔC18	IAGERRYGTIYQGRLWAF	[14]
24	HNP-1ΔC18A	IAAERRYATIYQARLWAF	[14]
25	HNP-1ΔC	AYRIPAIAGERRYGTIYQGRLWAF	[14]
27	K4S4 (1–16)a	ALWKTLLKKVLKAA	[15]
41	S4 (6–28)	TLLKKVLKAAAKAALNAVLVG	[15]
28	LfcinB	FKCRRWQWRMKKLGAPSITCVRRAF	[16]
49	AVP 1093	RRKKALLALLAP	[16]
50	AVP 1074	RRKKAAVALLPAVLLA	[16]
51	AVP 1092	RRKKPAVLLALLAP	[16]
52	AVP 1072	RRKKAAVALLPAVLLALL	[16]
53	AVP 1070	RRKKAAVALLPAVLLALLLAP	[16]
29	Limandapleu-rocidin(LmPle)	GWKKWFKKATHVGKHVGKAALDAYL	[17]
30	MRP	AIGSILGALAKGLPTLISWIKNR	[18]
31	MSI-78	GIGKFLKKAKKFGKAFVKILKK	[19]
33	Magainin I	GIGKFLHSAGKFGKAFVGEIMKS	[20]
34	Magainin II	GIGKFLHSAKKFGKAFVGEIMNS	[20]
35	P1	WLVFFVIFYFFR	[21]
36	P2	WLVFFVIFYIFR	[21]
39	RTD1	GFCRCLCRRGVCRCICTR	[21]
42	TAT-C	GRKKRRQRRRC	[22]
55	STAT 1	CTAGACTTCAGACCACACAAC	[23]
56	STAT 2	GAGGAGAAGCAATGGGTCTTAG	[23]
57	GAPdH	CACATGGCCTCCAAGGAGTAA	[23]
58	Mx 1	AAGCCTGATCTGGTGGACAAAGGA	[23]
6	B	VPKFKAGKILKQKVEKG	[9]
7	BR-C	CKLKNFAKGVAQSLLNKASKLSGQC	[9]
8	BR-D	KLKNFAKGVAQSLLNKASCKLSGQC	[9]

12	Brevinin-2R	KLKNFAKGVAQSLLNKASCKLSGQC	**[9]**
59	GLK-19	GLKKLLGKLLKKLGKLLLK	**[24]**
60	GLR-19	GLRRLLGRLLRRLGRLLLR	**[24]**
61	GLRC-1	GCRRLLGRLLRRLGRLLCR	**[24]**
62	GLRC-2	GLRCRLGRLLRR LGRCLLR	**[24]**
63	GLRC-3	GLRRLCGRLGRRLCRLLLR	**[24]**
64	GLRC-4	GCRRLCGRLGRRLCRLLCR	**[24]**

2.2. Varicella Zoster Virus Targets

Three VZV molecules were taken from protein databank website (http://www.rcsb.org/pdb/home/home.do) used in molecular docking experiment as drug targets, these molecules listed in Table 2:

Table (2): Viral molecules target with their three-dimensional structure

No.	Viral molecules	Structure	Ref.
1	Envelope glycoprotein H target (PDBID: 4XHJ)		[25]
2	Thymidine kinase target (PDBID: 1OSN)		[26]
3	Protease target (PDBID: 1VZV)		[27]

2.3. Methods

Several programs have been used to assess theoretical attachment of used short peptides against Varicella Zoster Virus, in addition to their physical and chemical properties. These programs are:

- Hex 8.0.0: Molecular docking of receptors and ligands, was done using this program [28].
- Pymol and Chimera software were used for results visualization [29].
- Pepstr server: Pepstr server predicts the tertiary structure of short peptides [30].
- T cell epitope: by which immunogenicity was predicted using T cell epitope (http://tools.immuneepitope.org/immunogenicity/)[31].
- ToxinPred: used for the estimation of peptides toxicity and chemical-physical properties (http://crdd.osdd.net/raghava/toxinpred/design.php) [32].
- CellPPD: was used to predict cell penetrating probability of peptides, it also predicts hydropathicity, isoelectric point (PI) and molecular weight. On the other hand, the hydrophobicity and hydrophilicity were directly related to the hydropathy index as reported by Kyte and Doolittle [33], CellPPD available at (http://crdd.osdd.net/raghava/cellppd/index.html)[34].
- The Boman index values test was performed; this test shows the ability of the peptide to bind with other proteins rather than the targets of protein it can be calculated according to the online Antimicrobial Peptide Database (http://aps.unmc.edu/AP/main.php) [35].

3. Results

Molecular docking for several peptides that set as AMP, these AMP collected from particular researches then investigated according to specific VZV targets including Thymidine kinase (PDBID: 1OSI), envelope glycoprotein H (PDPID: 4XHJ) and protease (PDBID: 1VZV) by a specific program Hex.

3.1. Molecular docking of selected peptides with Envelope glycoprotein H target (PDPID: 4XHJ)

Envelope glycoprotein H docked with AMP as shown in Table 3 the delta G values, or energy values (E-value) arranged from the lowest energy value to highest. From 64 peptides only 22 peptides are selected to be the lowest energy value, from the lowest one (MSI-78) its'E-value (-791.49 Kcal/mol) to the highest selected one (brevinin-1BYa) its'E-value (-507.62 Kcal/mol).

Table (3): Energy value of selected peptides attached with envelope glycoprotein H target (PDBID: 4XHJ)

No	Molecule Name	Sequence	E-value (Kcal/ (mol
1	MSI-78	GIGKFLKKAKKFGKAFVKILKK	-791.49
2	A	VVKKARKAAKKVAKK	-725.94
3	Androctonin	RSVCRQIKICRRRGGCYYKCTNRPY	-715.35
4	TAT-C	GRKKRRQRRRC	-653.67
5	GLRC-2	GLRCRLGRLLRR LGRCLLR	-648.08
6	Polyphemusin 2	RRWCFRVCYKGFCYRKCR	-597.55
7	K4S4(1-16)a	ALWKTLLKKVLKAA	-596.65
8	GLRC-1	GCRRLLGRLLRRLGRLLCR	-596.03
9	Lfcin B	FKCRRWQWRMKKLGAPSITCVRRAF	-594.88
10	GLRC-3	GLRRLCGRLGRRLCRLLLR	-592.09
11	GLK-19	GLKKLLGKLLKKLGKLLLK	-589.28
12	GLRC-4	GCRRLCGRLGRRLCRLLCR	-583.16
13	Fv16	KKVGTSKVVAKTVTKK	-582.14
14	Limandapleu-(rocidin(LmPle	GWKKWFKKATHVGKHVGKAALDAYL	-581.17
15	BR-C	CKLKNFAKGVAQSLLNKASKLSGQC	-549.89
16	D	AIRRLARRGGVKRISGLI	-545.19
17	B	VPKFKAGKILKQKVEKG	-543.06
18	GLR-19	GLRRLLGRLLRRLGRLLLR	-541.15
19	S4a	TLLKKVLKAAAKAALNAVLVG	-539.54
20	Tachyplesin 1	KWCFRVCYRGICYRRCR	-520.54
21	Brevinin-1BYb	FLPILASLAAKLGPKLFCLVTKKC	-513.22
22	Brevinin-1BYa	FLPILASLAAKFGPKLFCLVTKKC	-507.62
23	Brevinin-2R	KLKNFAKGVAQSLLNKASCKLSGQC	-495.28
24	C	TGKIGKLKKGTGKIA	-493.16
25	AVP 1070	RRKKAAVALLPAVLLALLLAP	-489.79
26	MRP	AIGSILGALAKGLPTLISWIKNR	-487.93
27	RTD 1	GFCRCLCRRGVCRCICTR	-482.88
28	Brevinin-1BYc	FLPILASLAATLGPKLLCLITKKC	-470.52
29	Protegrin PG-1	RGGRLCYCRRRFCVCVGR	-470.41
30	AVP 1072	RRKKAAVALLPAVLLALL	-457.49
31	CP11	ILKKWPWWPWRRK	-456.91
32	Magainin 2	GIGKFLHSAKKFGKAFVGEIMNS	-454.95
33	AVP 1093	RRKKALLALLAP	-451.36
34	Caerin 4.1	GLWQKIKSAAGDLASGIVEGIKS	-441.03
35	Vperin 3.6	GVIDAAKKWNVLKNLF	-433.25

36	Dahlein5.6	GLLASLGKVFGGYLAEKLKPK	-429.57
37	AVP 1092	RRKKPAVLLALLAP	-419.46
38	AVP 1074	RRKKAAVALLPAVLLA	-417.46
39	F	KATKATITKKPVA	-412.62
40	Magainin 1	GIGKFLHSAGKFGKAFVGEIMKS	-410.62
41	HNP-1C	AYRIPAIAGERRYGTIYQGRLWAF	-396.29
42	HNP-1C-18A	IAAERRYATIYQARLWAF	-386.45
43	CP10A	ILAWKWAWWAWRR	-368.96
44	Indolicidin	ILPWKWPWWPWRR	-358.66
45	Ranatuerin 6	FISAIASMLGKFL	-354.21
46	HNP-1C-18	IAGERRYGTIYQGRLWAF	-353.17
47	Aurein 1	GLFDIIKKIAESF	-351.63
48	Caerin 1.1	GLLSVLGSVAKHVLPHVVPVIAEHL	-344.07
49	Caerin 1.9	GLFGVLGSIAKHVLPHVVPVIAEKL	-341.62
50	Maculatin 1-1	GLFGVLAKVAAHVVPAIAEHF	-332.89
51	Citropin 1.1	GLFDVIKKVASVIGGL	-323.20
52	DET3	IGVRPGKLDL	-320.28
53	DET1	GWVKPAKLDG	-310.85
54	DET4	AGVKDGKLDF	-307.41
55	STAT 1	CTAGACTTCAGACCACACAAC	-302.93
56	Mx 1	AAGCCTGATCTGGTGGACAAAGGA	-298.40
57	BR-D	KLKNFAKGVAQSLLNKASCKLSGQC	-296.92
58	P1	WLVFFVIFYFFR	-285.42
59	P2	WLVFFVIFYIFR	-280.77
60	GAPdH	CACATGGCCTCCAAGGAGTAA	-274.34
61	Alloferon 2	GVSGHGQHGVHG	-273.30
62	STAT 2	GAGGAGAAGCAATGGGTCTTAG	-265.15
63	DET2	PWLKPGDLDL	-221.29
64	Alloferon 1	HGVSGHGQHGVHG	-214.73
Indicated to the lowest selected energy value of peptide			

Then these 22 AMP treated with other online programs to predict its characteristic, including cell penetration, PI, Boman index, hydropathicity, and molecular weight as shown in Table 4. The cell penetration test shows good penetration probability for some selected peptides, so from 22 peptides about 16 peptides could penetrate into the cell (The cell penetrated one, has a positivE-value of the SVM score (Yellowish color). In addition, this Table shows hydropathicity values, the peptide that has more hydpathicity value than 1or less than -1, it will be neglected, and so from 16 peptides 13 peptides pass the hydropathicity test.

Table (4): Predicted cell penetration, isoelectric point, Boman index, hydropathicity and molecular weight values for the selected AMP with envelope glycoprotein H target.

.No	Molecule\ Name	Cell penetration Prediction	SVM Score of cell penetration	PI	Boman index (kcal/ (mol	Hydropathicity (Kcal/mol)	Mol. wt (Dalton)
1	MSI-78	CPP	0.46	10.91	0.49	-0.16	2478.54
2	A	CPP	0.51	11.48	2.29	-0.80	1653.34
3	Androctonin	Non-CPP	-0.12	10.23	3.93	-1.06	3081.01
4	TAT-C	CPP	1.52	12.31	9.44	-3.29	1499.95
5	GLRC-2	CPP	0.47	12.13	3.4	-0.06	2281.17
6	K4S4(1-16)a	CPP	0.41	10.49	-0.47	0.54	1583.25
7	GLRC-1	CPP	0.35	12.13	3.4	-0.06	2281.17
8	Lfcin B	CPP	0.18	11.85	2.75	-0.58	3126.17
9	GLRC-3	CPP	0.32	12.13	3.4	-0.06	2281.17
10	GLK-19	CPP	0.41	10.78	-0.43	0.30	2105.16
11	GLRC-4	CPP	0.23	11.61	3.78	-0.19	2261.11
12	Fv16	CPP	0.02	10.71	1.59	-0.51	1702.35
13	Limandapleurocidin(LmPle)	Non-CPP	-0.18	10.13	0.73	-0.49	2840.75
14	Polyphemusin 2	CPP	0.27	10.11	3.75	-0.80	2431.19
15	BR-C	Non-CPP	-0.24	9.91	1.02	-0.16	2637.53
16	D	Non-CPP	-0.18	12.61	2.69	0.03	1992.72
17	B	Non-CPP	-0.18	10.31	1.23	-0.68	1898.63
18	GLR-19	CPP	0.47	12.78	3.01	0.08	2301.23
19	S4a	Non-CPP	-0.31	10.49	-0.81	1.06	2092.96
20	Tachyplesin 1	CPP	0.05	9.94	3.53	-0.52	2268.99
21	Brevinin-1BYb	CPP	0.02	9.72	-1.04	1.12	2575.66
22	Brevinin-1BYa	CPP	0.02	9.72	-0.96	1.08	2609.67

Indicated to the peptide that could perpetrated to cell.
Indicated to peptide excepted value for hydropathicity.

Furthermore, Table 5 shows the prediction of immunogenicity by class I immunogenicity test. From these 13 peptides only 6 peptides pass the immunogenicity test, and all these 6 peptides predicted to be non-toxic by toxicity prediction test. So these 6 peptides predicted to be effective against VZV.

Table (5): Predicted immunogenicity and toxicity of selected antimicrobial peptides with the envelope glycoprotein H target.

.No	Molecule Name	Score Class I Immunogenicity	Toxicity Prediction	SVM score of toxicity
1	MSI-78	-0.99548	Non-Toxin	-0.86
2	A	-0.80642	Non-Toxin	-0.65
3	GLRC-2	0.17076	Non-Toxin	-1.25
4	K4S4(1-16)a	-0.67828	Non-Toxin	-1.48
5	GLRC-1	0.23118	Non-Toxin	-1.35
6	Lfcin B	0.02174	Non-Toxin	-0.92
7	GLRC-3	0.1728	Non-Toxin	-1.35
8	GLK-19	-1.14128	Non-Toxin	-1.14
9	GLRC-4	0.14778	Non-Toxin	-1.41
10	Fv16	-0.39388	Non-Toxin	-1.31
11	Polyphemusin 2	-0.11773	Non-Toxin	-0.19
12	GLR-19	0.2562	Non-Toxin	-1.14
13	Tachyplesin 1	0.3526	Non-Toxin	-1.15

Indicated to non-immunogenic peptide.
Indicated to non-toxic peptide.

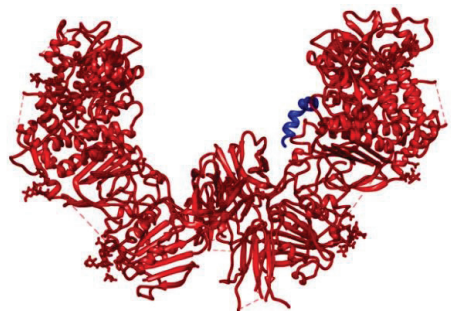
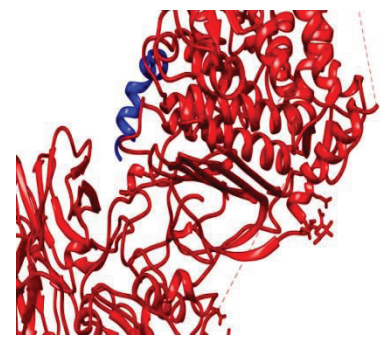
Then the selected 6 peptides sorted according to the lowest energy value to the highest one with the other properties of peptide as shown in Table 6. Furthermore the selected 6 peptide were sorted according to Boman index value and the molecular.

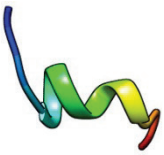
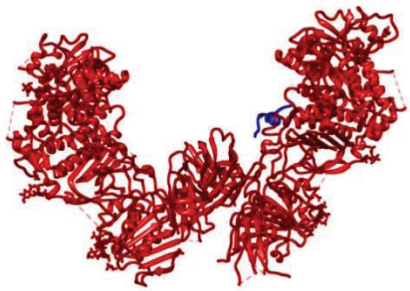
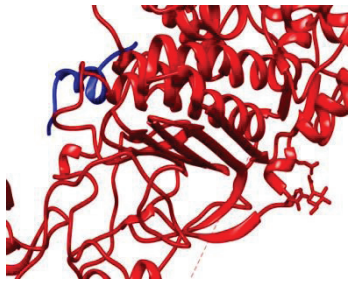
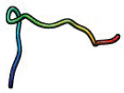
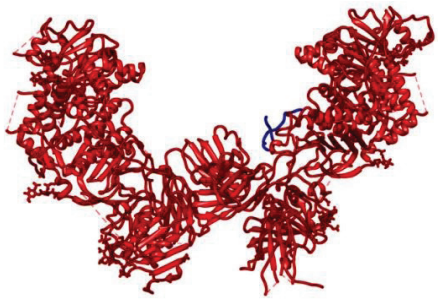
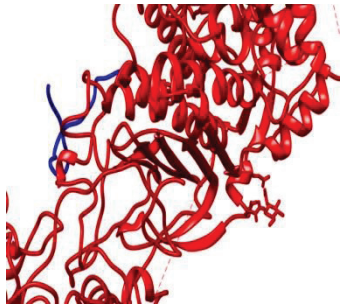
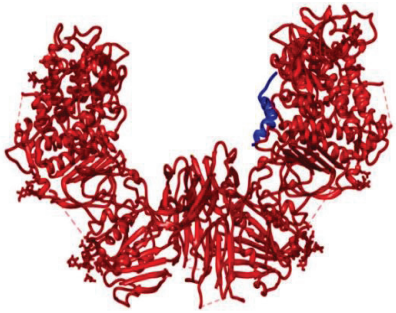
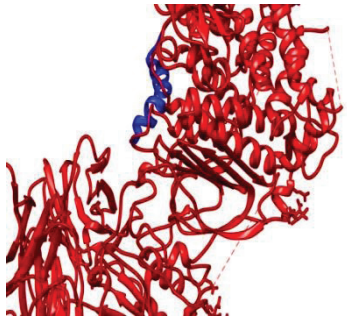
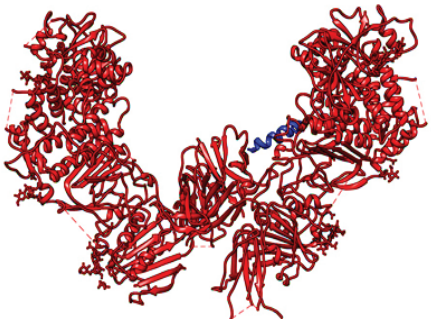
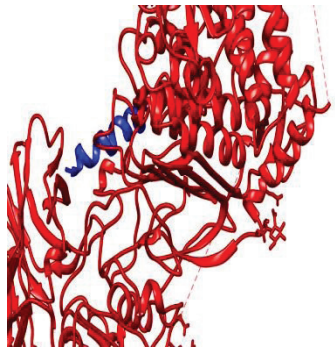
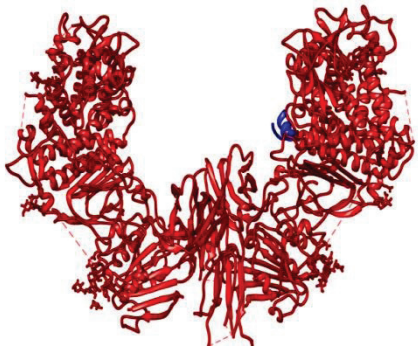
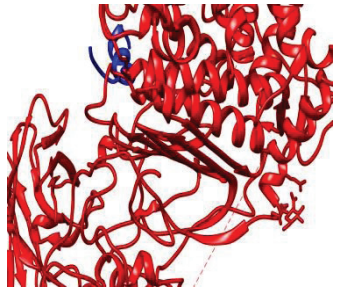
Table (6): Peptides with the lowest E-values of an envelope glycoprotein H target (PDBID: 4XHJ), and their prediction of cell penetration, immunogenicity, toxicity, isoelectric point, Bomam index, hydropathicity and molecular weight. Sorted according E-values.

.No	Molecule Name	E-value (kcal/mol)	Cell penetration Prediction	SVM Score of cell penetration	Class I Immunogenicity	Toxicity Prediction	SVM score of Toxicity	pI	Boman index (kcal/mol)	Hydropathicity(kcal/mol)	Molwt (Dalton)
1	MSI-78	-791.49	CPP	0.46	-0.99548	Non-Toxin	-0.86	10.91	0.49	-0.16	2478.54
2	A	-725.94	CPP	0.51	-0.80642	Non-Toxin	-0.65	11.48	2.29	-0.80	1653.34
3	Polyphemusin 2	-597.55	CPP	0.27	-0.11773	Non-Toxin	-0.19	10.11	3.75	-0.80	2431.19
4	K4S4(1-16)a	-596.65	CPP	0.41	-0.67828	Non-Toxin	-1.48	10.49	-0.47	0.54	1583.25
5	GLK-19	-589.28	CPP	0.41	-1.14128	Non-Toxin	-1.14	10.78	-0.43	0.30	2105.16
6	Fv16	-582.14	CPP	0.02	-0.39388	Non-Toxin	-1.31	10.71	1.59	-0.51	1702.35
Indicated to energy value from lowest to highest values.											

Finally, Table 7 shows the three-dimensional structures of these 6 selected peptides with their binding site to their proposed target; envelope glycoprotein H; and docking were done using Hex 8.0.0 software.

Table (7): The three-dimensional structures of selected antimicrobial peptides with their binding site on their proposed envelope glycoprotein H target (PBBID: 4XHJ), docking was done using Hex 8.0.0 software.

.NO	Molecule Name	Envelope glycoprotein H (4XHJ) - peptides complex	Focus docking
1	 MSI-78		

2	 A		
3	Polyphemusin 2 		
4	K4S4(1-16)a 		
5	GLK-19 		
6	Fv16 		

3.2 Molecular docking of selected antimicrobial peptides with thymidine kinase target (PDBID: 1OSN)

Thymidine kinase target docked with peptides as shown in Table 8 the E-value arranged in ascending order. From 64 peptides only 27 peptides were selected to be the lowest energy value, from the lowest one MSI-78 its' E-value -1027.32 Kcal/mol to the highest selected one AVP 1072 it is E-value -800.62 Kcal/mol.

Table (8): Energy value of selected antimicrobial peptides attached with thymidine kinase target (PDBID: 1OSN)

No	Molecule Name	Sequence	E-value (Kcal/mol)
1	MSI-78	GIGKFLKKAKKFGKAFVKILKK	-1027.32
2	A	VVKKARKAAKKVAKK	-967.51
3	GLRC-3	GLRRLCGRLGRRLCRLLLR	-905.46
4	GLRC-2	GLRCRLGRLLRR LGRCLLR	-902.08
5	Androctonin	RSVCRQIKICRRRGGCYYKCTNRPY	-886.84
6	GLK-19	GLKKLLGKLLKKLGKLLLK	-883.56
7	Fv16	KKVGTSKVVAKTVTKK	-882.43
8	Polyphemusin 2	RRWCFRVCYKGFCYRKCR	-876.07
9	GLRC-1	GCRRLLGRLLRRLGRLLCR	-869.31
10	AVP 1092	RRKKPAVLLALLAP	-860.48
11	Lfcin B	FKCRRWQWRMKKLGAPSITCVRRAF	-858.07
12	TAT-C	GRKKRRQRRRC	-855.35
13	AVP 1074	RRKKAAVALLPAVLLA	-848.62
14	BR-D	KLKNFAKGVAQSLLNKASCKLSGQC	-841.01
15	Brevinin-2R	KLKNFAKGVAQSLLNKASCKLSGQC	-841.01
16	Magainin 1	GIGKFLHSAGKFGKAFVGEIMKS	-840.59
17	F	KATKATITKKPVA	-837.74
18	Protegrin PG-1	RGGRLCYCRRRFCVCVGR	-832.00
19	K4S4(1-16)a	ALWKTLLKKVLKAA	-827.8
20	Limandapleu-(rocidin(LmPle	GWKKWFKKATHVGKHVGKAALDAYL	-822.71
21	AVP 1070	RRKKAAVALLPAVLLALLLAP	-815.91
22	C	TGKIGKLKKGTGKIA	-812.93
23	CP10A	ILAWKWAWWAWRR	-812.93
24	GLR-19	GLRRLLGRLLRRLGRLLLR	-812.27
25	Tachyplesin 1	KWCFRVCYRGICYRRCR	-809.53
26	Dahlein5.6	GLLASLGKVFGGYLAEKLKPK	-803.68
27	AVP 1072	RRKKAAVALLPAVLLALL	-800.62

28	D	AIRRLARRGGVKRISGLI	-798.49
29	S4a	TLLKKVLKAAAKAALNAVLVG	-795.68
30	CP11	ILKKWPWWPWRRK	-763.61
31	AVP 1093	RRKKALLALLAP	-747.25
32	Brevinin-1BYb	FLPILASLAAKLGPKLFCLVTKKC	-747.08
33	Caerin 1.9	GLFGVLGSIAKHVLPHVVPVIAEKL	-746.54
34	Brevinin-1BYc	FLPILASLAATLGPKLLCLITKKC	-741.05
35	Brevinin-1BYa	FLPILASLAAKFGPKLFCLVTKKC	-735.59
36	B	VPKFKAGKILKQKVEKG	-733.19
37	HNP-1C	AYRIPAIAGERRYGTIYQGRLWAF	-732.21
38	MRP	AIGSILGALAKGLPTLISWIKNR	-703.66
39	Magainin 2	GIGKFLHSAKKFGKAFVGEIMNS	-699.17
40	HNP-1C-18A	IAAERRYATIYQARLWAF	-698.07
41	RTD 1	GFCRCLCRRGVCRCICTR	-697.41
42	HNP-1C-18	IAGERRYGTIYQGRLWAF	-664.99
43	Citropin 1.1	GLFDVIKKVASVIGGL	-664.75
44	Ranatuerin 6	FISAIASMLGKFL	-659.47
45	Vperin 3.6	GVIDAAKKWNVLKNLF	-656.30
46	Maculatin 1-1	GLFGVLAKVAAHVVPAIAEHF	-649.71
47	Caerin 4.1	GLWQKIKSAAGDLASGIVEGIKS	-639.73
48	Indolicidin	ILPWKWPWWPWRR	-618.09
49	Caerin 1.1	GLLSVLGSVAKHVLPHVVPVIAEHL	-601.06
50	Aurein 1	GLFDIIKKIAESF	-561.93
51	GAPdH	CACATGGCCTCCAAGGAGTAA	-543.67
52	DET4	AGVKDGKLDF	-523.02
53	STAT 1	CTAGACTTCAGACCACACAAC	-521.32
54	P1	WLVFFVIFYFFR	-511.13
55	STAT 2	GAGGAGAAGCAATGGGTCTTAG	-502.79
56	DET2	PWLKPGDLDL	-493.49
57	DET3	IGVRPGKLDL	-491.53
58	DET1	GWVKPAKLDG	-484.01
59	Alloferon 1	HGVSGHGQHGVHG	-471.02
60	Alloferon 2	GVSGHGQHGVHG	-467.14
61	GLRC-4	GCRRLCGRLGRRLCRLLCR	-424.64
62	BR-C	CKLKNFAKGVAQSLLNKASKLSGQC	-353.71
63	Mx 1	AAGCCTGATCTGGTGGACAAAGGA	-226.49
64	P2	WLVFFVIFYIFR	543.98
Indicated to the lowest selected energy value of peptide			

Table (9): Predicted cell penetration, isoelectric point, Boman index, hydropathicity and molecular weight values for the selected peptides attached well with thymidine kinase target (PDBID: 1OSN).

.No	Molecule Name	Cell penetration Prediction	SVM Score of cell penetration	PI	Boman index ((kcal/mol	Hydropathicity (kcal/mol)	Molwt (Dalton)
1	MSI-78	CPP	0.46	10.91	0.49	-0.16	2478.54
2	A	CPP	0.51	11.48	2.29	-0.80	1653.34
3	GLRC-3	CPP	0.32	12.13	3.4	-0.06	2281.17
4	GLRC-2	CPP	0.47	12.13	3.4	-0.06	2281.17
5	Androctonin	Non-CPP	-0.12	10.23	3.93	-1.06	3081.01
6	GLK-19	CPP	0.41	10.78	-0.43	0.30	2105.16
7	Fv16	CPP	0.02	10.71	1.59	-0.51	1702.35
8	Polyphemusin 2	CPP	0.27	10.11	3.75	-0.80	2431.19
9	GLRC-1	CPP	0.35	12.13	3.4	-0.06	2281.17
10	AVP 1092	CPP	0.48	12.02	0.84	0.34	1546.18
11	Lfcin B	CPP	0.18	11.85	2.75	-0.58	3126.17
12	TAT-C	CPP	1.52	12.31	9.44	-3.29	1499.95
13	AVP 1074	CPP	0.03	12.02	0.25	0.89	1690.38
14	BR-D	Non-CPP	-0.14	9.91	1.02	-0.16	2637.53
15	Brevinin-2R	Non-CPP	-0.14	9.91	1.02	-0.16	2637.53
16	Magainin 1	CPP	0.25	10.01	0.08	0.22	2410.23
17	F	CPP	0.41	10.49	1.19	-0.40	1356.85
18	Protegrin PG-1	CPP	0.39	10.67	3.65	-0.25	2160.87
19	K4S4(1-16)a	CPP	0.41	10.49		0.54	1583.25
20	Limandapleu-rocidin(LmPle)	Non-CPP	-0.18	10.13	0.73	-0.49	2840.75
21	AVP 1070	CPP	0.09	12.02	-0.59	1.23	2198.14
22	C	Non-CPP	-0.18	10.61	0.83	-0.53	1500.10
23	CP10A	CPP	0.19	12.01	0.65	-0.28	1829.37
24	GLR-19	CPP	0.47	12.78	3.01	0.08	2301.23
25	Tachyplesin 1	CPP	0.05	9.94	3.53	-0.52	2268.99
26	Dahlein5.6	CPP	0.05	9.84	-0.3	0.25	2190.00
27	AVP 1072	Non-CPP	-0.20	12.02	-0.31	1.21	1916.74

.Indicated to the peptide that could perpetrated to cell

.Indicated to peptide excepted value for hydropathicity

After that, Table 10, shows the prediction of immunogenicity by class I immunogenicity test. From these 19 peptides; only 11 peptides were pass the immunogenicity test, and all these 11 peptides predicted to be non-toxic by toxicity prediction test. So these 11 peptides predicted to be effective against VZV.

Table (10): Predicted immunogenicity and toxicity of selected peptides attached well to thymidine kinase target (PDBID: 1OSN).

No.	Molecule Name	Score Class I Immunogenicity	Toxicity Prediction	SVM score of toxicity
1	MSI-78	-0.99548	Non-Toxin	-0.86
2	A	-0.80642	Non-Toxin	-0.65
3	GLRC-3	0.1728	Non-Toxin	-1.35
4	GLRC-2	0.17076	Non-Toxin	-1.25
5	GLK-19	-1.14128	Non-Toxin	-1.14
6	Fv16	-0.39388	Non-Toxin	-1.31
7	Polyphemusin 2	-0.11773	Non-Toxin	-0.19
8	GLRC-1	0.23118	Non-Toxin	-1.35
9	AVP 1092	-0.19994	Non-Toxin	-1.45
10	Lfcin B	0.02174	Non-Toxin	-0.92
11	AVP 1074	-0.10378	Non-Toxin	-1.62
12	Magainin 1	-0.26042	Non-Toxin	-1.03
13	F	-0.35934	Non-Toxin	-1.28
14	Protegrin PG-1	0.20047	Non-Toxin	-0.48
15	K4S4(1-16)a	-0.67828	Non-Toxin	-1.48
16	CP10A	0.9648	Non-Toxin	-0.82
17	GLR-19	0.2562	Non-Toxin	-1.14
18	Tachyplesin 1	0.3526	Non-Toxin	-1.15
19	Dahlein5.6	-0.38065	Non-Toxin	-1.39

.Indicated to non-immunogenic peptide
Indicated to non-toxic peptide

Then the selected 11 peptides sorted according to the lowest energy value to the highest one with the other properties of peptide as shown in Table 11. Furthermore the selected 11 peptides sorted according to Boman index value and according to the molecular weight.

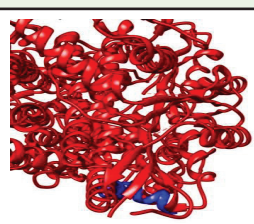
Table (11): Peptides with the lowest E-values of binding to thymidine kinase target (PDBID: 1OSN), and their prediction of cell penetration, immunogenicity, toxicity, isoelectric point, Bomam index, hydropathicity and molecular weight. Sorted according E-values.

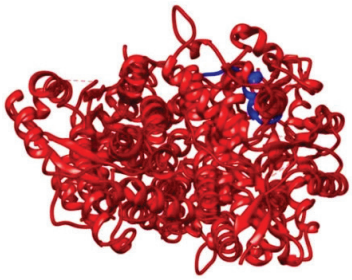
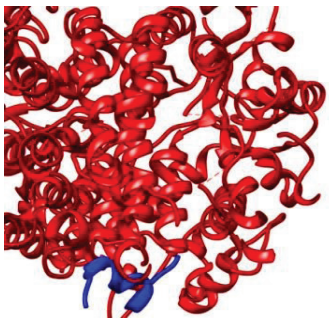
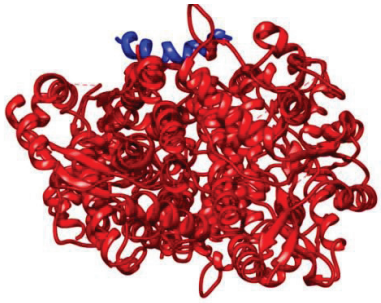
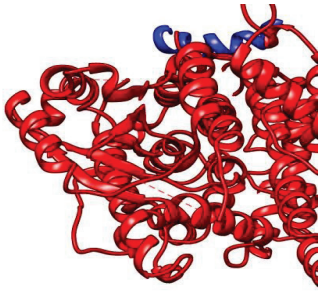
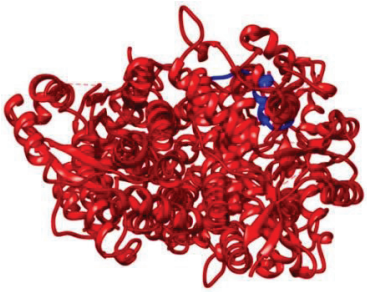
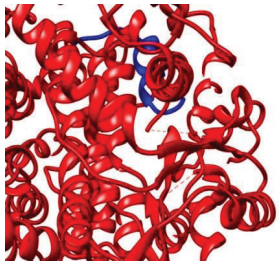
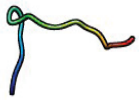
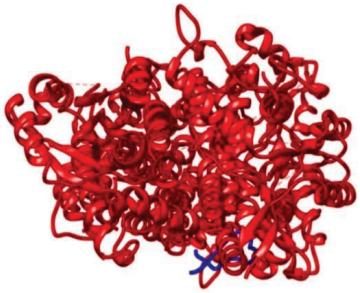
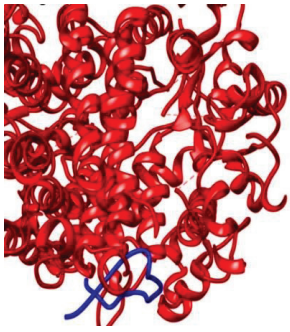
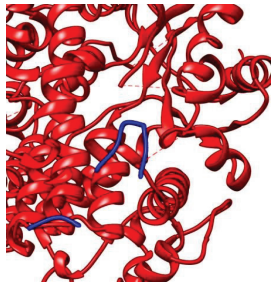
No	Molecule Name	E-value (kcal/mol)	Cell penetration Prediction	SVM Score of cell penetration	Score Class I Immunogenicity	Toxicity Prediction	SVM score of Toxicity	pI	Boman index (kcal/mol	Hydropathicity (kcal/mol)	Molwt (Dalton)
1	MSI-78	-1027.32	CPP	0.46	-0.99548	Non-Toxin	-0.86	10.91	0.49	-0.16	2478.54
2	A	-967.51	CPP	0.51	-0.80642	Non-Toxin	-0.65	11.48	2.29	-0.80	1653.34
3	GLK-19	-883.56	CPP	0.41	-1.14128	Non-Toxin	-1.14	10.78	-0.43	0.30	2105.16
4	Fv16	-882.43	CPP	0.02	-0.39388	Non-Toxin	-1.31	10.71	1.59	-0.51	1702.35
5	Polyphemusin 2	-876.07	CPP	0.27	-0.11773	Non-Toxin	-0.19	10.11	3.75	-0.80	2431.19
6	AVP 1092	-860.48	CPP	0.48	-0.19994	Non-Toxin	-1.45	12.02	0.84	0.34	1546.18
7	AVP 1074	-848.62	CPP	0.03	-0.10378	Non-Toxin	-1.62	12.02	0.25	0.89	1690.38
8	Magainin 1	-840.59	CPP	0.25	-0.26042	Non-Toxin	-1.03	10.01	0.08	0.22	2410.23
9	F	-837.74	CPP	0.41	-0.35934	Non-Toxin	-1.28	10.49	1.19	-0.40	1356.85
10	K4S4(1-16)a	-827.8	CPP	0.41	-0.67828	Non-Toxin	-1.48	10.49	-0.47	0.54	1583.25
11	Dahlein5.6	-803.68	CPP	0.05	-0.38065	Non-Toxin	-1.39	9.84	-0.3	0.25	2190.00
Indicated to energy value from lowest to highest values.											

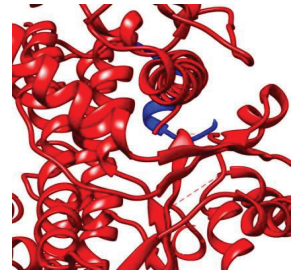
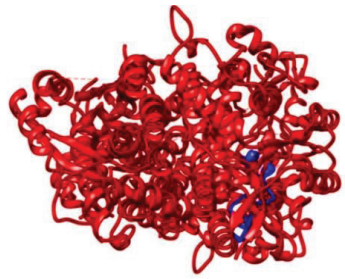
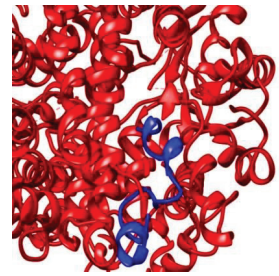
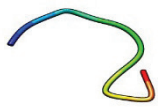
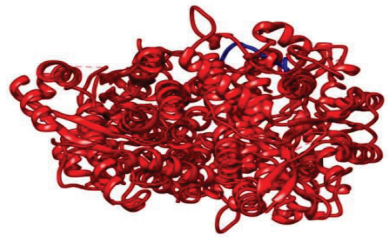
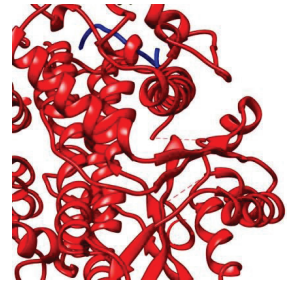
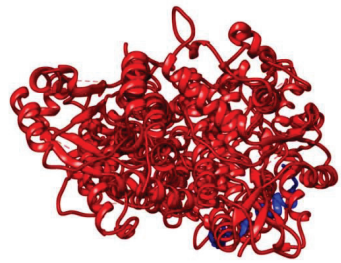
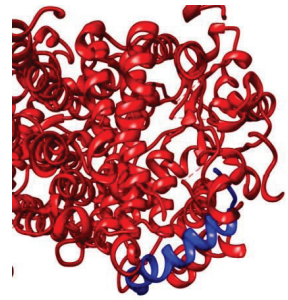
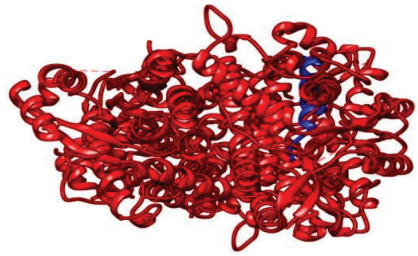
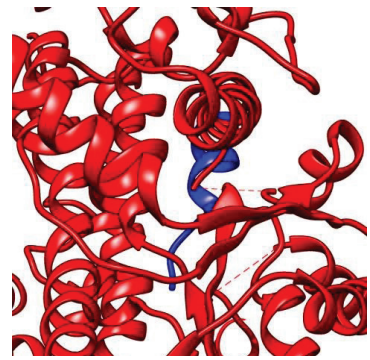
Finally, a

Table (12): shows the three-dimensional structures (by Chimera software) of these 11 selected peptides with their binding site to their proposed target; thymidine kinase; and docking was done using Hex 8.0.0 software.

Table (12): The three-dimensional structures of selected peptides with their binding site on their predicted thymidine kinase target (PDBID: 1OSN), docking is done using Hex software

No.	Molecule Name	Thymidine kinase target (1OSN) – peptides complex	Focus docking
1	MSI-78		

2	A 		
3	GLK-19 		
4	Fv16 		
5	Polyphemusin 2 		
6	AVP 1092 		

7	AVP 1074 		
8	Magainin 1 		
9	F 		
10	K4S4(1-16)a 		
11	Dahlein5.6 		

3.3. Molecular docking of selected peptides with Protease target (PDBID: 1VZV)

The VZV Protease docked with peptides as shown in Table 13 the E-value arranged from the lower energy value to highest. From 64 peptides only 20 peptides are selected to be the lowest energy value, from the lowest one (Lfcin B) its' E-value (-659.51Kcal/mol) to the highest selected one CP11 its' E-value -598.73Kcal/mol.

Table (13): Molecular docking of selected peptides with Protease target (PDBID: 1VZV)

No	Molecule Name	Sequence	E-value (Kcal/ (mol
1	Lfcin B	FKCRRWQWRMKKLGAPSITCVRRAF	-659.51
2	MSI-78	GIGKFLKKAKKFGKAFVKILKK	-643
3	BR-D	KLKNFAKGVAQSLLNKASCKLSGQC	-642.58
4	Brevinin-2R	KLKNFAKGVAQSLLNKASCKLSGQC	-642.58
5	GLRC-2	GLRCRLGRLLRR LGRCLLR	-635.92
6	K4S4(1-16)a	ALWKTLLKKVLKAA	-632.87
7	AVP 1070	RRKKAAVALLPAVLLALLLAP	-632.48
8	Caerin 1.9	GLFGVLGSIAKHVLPHVVPVIAEKL	-632.38
9	C	TGKIGKLKKGTGKIA	-628.07
10	Androctonin	RSVCRQIKICRRRGGCYYKCTNRPY	-620.20
11	Magainin 1	GIGKFLHSAGKFGKAFVGEIMKS	-617.97
12	MRP	AIGSILGALAKGLPTLISWIKNR	-614.03
13	A	VVKKARKAAKKVAKK	-611.60
14	STAT 1	CTAGACTTCAGACCACACAAC	-610.34
15	Limandapleu-(rocidin(LmPle	GWKKWFKKATHVGKHVGKAALDAYL	-606.32
16	AVP 1074	RRKKAAVALLPAVLLA	-605.48
17	AVP 1072	RRKKAAVALLPAVLLALL	-604.52
18	Brevinin-1BYa	FLPILASLAAKFGPKLFCLVTKKC	-602.12
19	GLRC-1	GCRRLLGRLLRRLGRLLCR	-598.88
20	CP11	ILKKWPWWPWRRK	-598.73
21	Caerin 4.1	GLWQKIKSAAGDLASGIVEGIKS	-598.08
22	BR-C	CKLKNFAKGVAQSLLNKASKLSGQC	-593.08
23	Brevinin-1BYb	FLPILASLAAKLGPKLFCLVTKKC	-588.70
24	GLK-19	GLKKLLGKLLKKLGKLLLK	-588.66

25	GLRC-3	GLRRLCGRLGRRLCRLLLR	-582.37
26	Maculatin 1-1	GLFGVLAKVAAHVVPAIAEHF	-572.91
27	D	AIRRLARRGGVKRISGLI	-570.11
28	Ranatuerin 6	FISAIASMLGKFL	-569.85
29	HNP-1C-18	IAGERRYGTIYQGRLWAF	-568.98
30	GLRC-4	GCRRLCGRLGRRLCRLLCR	-567.25
31	B	VPKFKAGKILKQKVEKG	-565.01
32	HNP-1C	AYRIPAIAGERRYGTIYQGRLWAF	-562.57
33	Mx 1	AAGCCTGATCTGGTGGACAAAGGA	-559.58
34	AVP 1092	RRKKPAVLLALLAP	-557.72
35	Fv16	KKVGTSKVVAKTVTKK	-557.44
36	S4a	TLLKKVLKAAAKAALNAVLVG	-557.21
37	Brevinin-1BYc	FLPILASLAATLGPKLLCLITKKC	-550.42
38	Citropin 1.1	GLFDVIKKVASVIGGL	-549.84
39	Dahlein5.6	GLLASLGKVFGGYLAEKLKPK	-547.28
40	Vperin 3.6	GVIDAAKKWNVLKNLF	-544.72
41	GLR-19	GLRRLLGRLLRRLGRLLLR	-542.83
42	TAT-C	GRKKRRQRRRC	-541.96
43	Tachyplesin 1	KWCFRVCYRGICYRRCR	-541.09
44	Protegrin PG-1	RGGRLCYCRRRFCVCVGR	-539.44
45	AVP 1093	RRKKALLALLAP	-537.81
46	Magainin 2	GIGKFLHSAKKFGKAFVGEIMNS	-536.42
47	CP10A	ILAWKWAWWAWRR	-534.31
48	Polyphemusin 2	RRWCFRVCYKGFCYRKCR	-533.41
49	Caerin 1.1	GLLSVLGSVAKHVLPHVVPVIAEHL	-517.01
50	GAPdH	CACATGGCCTCCAAGGAGTAA	-507.75
51	STAT 2	GAGGAGAAGCAATGGGTCTTAG	-507.06
52	Aurein 1	GLFDIIKKIAESF	-505.53
53	F	KATKATITKKPVA	-501
54	HNP-1C-18A	IAAERRYATIYQARLWAF	-499.46
55	P1	WLVFFVIFYFFR	-491.62
56	DET2	PWLKPGDLDL	-490.71
57	Alloferon 1	HGVSGHGQHGVHG	-488.60

58	Indolicidin	ILPWKWPWWPWRR	-474.22
59	RTD 1	GFCRCLCRRGVCRCICTR	-473.18
60	P2	WLVFFVIFYIFR	-472.28
61	DET4	AGVKDGKLDF	-451.36
62	DET1	GWVKPAKLDG	-419.53
63	DET3	IGVRPGKLDL	-406.83
64	Alloferon 2	GVSGHGQHGVHG	-402.48
Indicated to the lowest selected energy value of peptide			

Then these 20 peptides were treated with other online programs to predict their characteristics, including cell penetration, isoelectric point, Boman index, hydropathicity, and molecular weight as shown in Table 14. The cell penetration test shows good penetration for some selected peptides, so from 20 peptides about 11 peptides can penetrate to cell. Also, this Table shows hydropathicity values.

Table (14): Predicted cell penetration, isoelectric point, Boman index, hydropathicity and molecular weight values of the selected peptides binds well to protease target (PDBID: 1VZV).

No.	Molecule Name	Prediction	SVM Score	PI	Boman index (kcal/(mol	Hydropathicity (kcal/mol)	Molwt (Dalton)
1	Lfcin B	CPP	0.18	11.85	2.75	-0.58	3126.17
2	MSI-78	CPP	0.46	10.91	0.49	-0.16	2478.54
3	BR-D	Non-CPP	-0.14	9.91	1.02	-0.16	2637.53
4	Brevinin-2R	Non-CPP	-0.14	9.91	1.02	-0.16	2637.53
5	GLRC-2	CPP	0.47	12.13	3.4	-0.06	2281.17
6	K4S4(1-16)a	CPP	0.41	10.49	-0.47	0.54	1583.25
7	AVP 1070	CPP	0.09	12.02	-0.59	1.23	2198.14
8	Caerin 1.9	Non-CPP	-0.52	8.94	-1.14	1.15	2594.59
9	C	Non-CPP	-0.18	10.61	0.83	-0.53	1500.10
10	Androctonin	Non-CPP	-0.12	10.23	3.93	-1.06	3081.01
11	Magainin 1	CPP	0.25	10.01	0.08	0.22	2410.23
12	MRP	Non-CPP	-0.22	11.17	-0.34	0.73	2393.28
13	A	CPP	0.51	11.48	2.29	-0.80	1653.34
14	STAT 1	Non-CPP	-0.37	5.70	0.89	1.50	1829.42
15	Limandapleurocidin(LmPle)	Non-CPP	-0.18	10.13	0.73	-0.49	2840.75

16	AVP 1074	CPP	0.03	12.02	0.25	0.89	1690.38
17	AVP 1072	Non-CPP	-0.20	12.02	-0.31	1.21	1916.74
18	Brevinin-1BYa	CPP	0.02	9.72	-0.96	1.08	2609.67
19	GLRC-1	CPP	0.35	12.13	3.4	-0.06	2281.17
20	CP11	CPP	0.42	12.03	2.1	-1.48	1880.51

.Indicated to the peptide that could perpetrated to cell

Indicated to peptide excepted value for hydropathicity

Table 15 shows the prediction of immunogenicity by class I immunogenicity test. From these 8 peptides, only 5 peptides pass the immunogenicity, and all these five peptides predicted to be non-toxic by toxicity prediction test. So these five peptides predicted to be effective against VZV.

Table (15): Predicted immunogenicity and toxicity of selected peptides with protease target (PDBID: 1VZV).

No.	Molecule Name	Score Class I Immunogenicity	Toxicity Prediction	SVM score of toxicity
1	Lfcin B	0.02174	Non-Toxin	-0.92
2	MSI-78	-0.99548	Non-Toxin	-0.86
3	GLRC-2	0.17076	Non-Toxin	-1.25
4	K4S4(1-16)a	-0.67828	Non-Toxin	-1.48
5	Magainin 1	-0.26042	Non-Toxin	-1.03
6	A	-0.80642	Non-Toxin	-0.65
7	AVP 1074	-0.10378	Non-Toxin	-1.62
8	GLRC-1	0.23118	Non-Toxin	-1.35

Indicated to non-immunogenic peptide.

Indicated to non-toxic peptide.

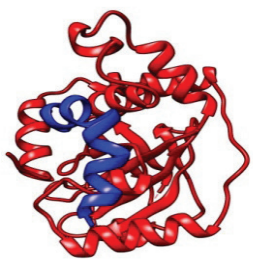
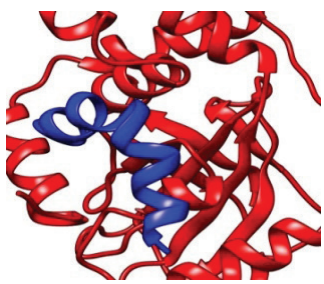
Then the selected 5 peptides sorted according to the lowest energy value to the highest one with the other properties of the peptide as shown in Table 16. Furthermore, the selected 5 peptides sorted according to Boman index value and according to the molecular weight.

Table (16): Peptides with the lowest E-values of binding to protease target (PDBID: 1VZV), and their prediction of cell penetration, immunogenicity, toxicity, isoelectric point, Bomam index, hydropathicity and molecular weight. Sorted according to E-values

No.	Molecule Name	E-value(kcal/mol)	Cell penetration Prediction	SVM Score of cell penetration	Score Class I Immunogenicity	Toxicity Prediction	SVM score of Toxicity	pI	(Boman index(kcal/mol	Hydropathicity(kcal/mol)	Molwt(Dalton)
1	MSI-78	-643	CPP	0.46	-0.99548	Non-Toxin	-0.86	10.49	0.49	-0.16	2478.54
2	K4S4(1-16)a	-632.87	CPP	0.41	-0.67828	Non-Toxin	-1.48	12.02	-0.47	0.54	1583.25
3	Magainin 1	-617.97	CPP	0.25	-0.26042	Non-Toxin	-1.03	11.48	0.08	0.22	2410.23
4	A	-611.60	CPP	0.51	-0.80642	Non-Toxin	-0.65	12.02	2.29	-0.80	1653.34
5	AVP 1074	-605.48	CPP	0.03	-0.10378	Non-Toxin	-1.62	9.72	0.25	0.89	1690.38
Indicated to energy value from lowest to highest values.											

Finally, Table 17 shows the three-dimensional structures (by Chimera software) of these 5 selected peptides with their binding site to their proposed target; Protease; and docking done using Hex 8.0.0 software.

Table (17): The three-dimensional structure of selected peptides with their binding site on their proposed protease target (PDBID: 1VZV), docking is done using Hex 8.0.0 software

No.	Molecule Name	Protease target (PDBID: 1VZV) –peptides complex	Focus docking
1	MSI-78 		

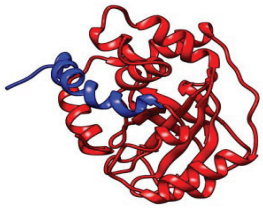
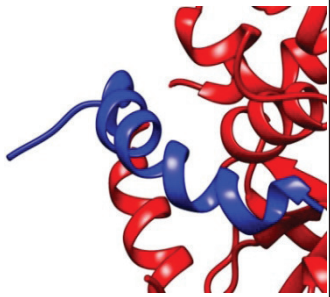
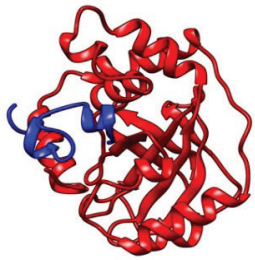
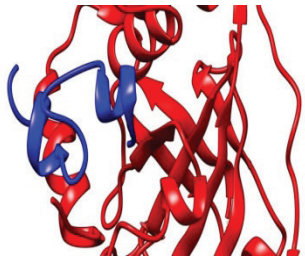
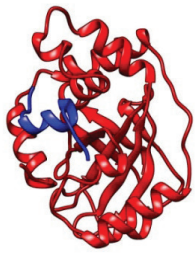
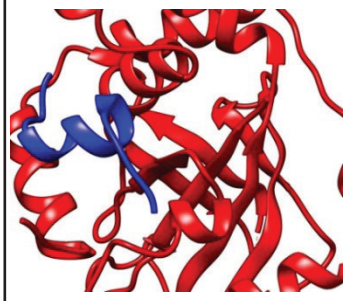
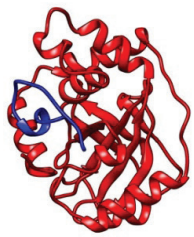
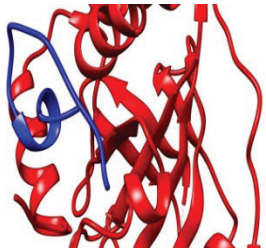
2	K4S4(1-16)a 		
3	Magainin 1 		
4	A 		
5	AVP 1074 		

Table (18): The ability of the selected peptides to bind with more than one VZV targets

No.	Molecule Name	Peptide Sequence	Target	E-value (Kcal/ (mo
1	Polyphemusin 2	RRWCFRVCYKGFCYRKCR	Envelope glycoprotein H (PDBID:4XHJ)	-597.55
			Thymidine kinase (PDBID: 1OSN)	-876.07

2	K4S4(1-16)a	ALWKTLLKKVLKAA	Envelope glycoprotein H (PDBID:4XHJ)	-596.65
			Thymidine kinase (1OSN)	-827.8
			Protease (PDBID:1VZ)	-632.87
3	F	KATKATITKKPVA	Thymidine kinase (PDBID: 1OSN)	-837.74
4	AVP 1092	RRKKPAVLLALLAP	Thymidine kinase (PDBID: 1OSN)	-860.48
5	MSI-78	GIGKFLKKAKKFGKAFVKILKK	Envelope glycoprotein H (PDBID:4XHJ)	-791.49
			Thymidine kinase (PDBID: 1OSN)	-1027.32
			Protease (PDBID:1VZ)	-643
6	A	VVKKARKAAKKVAKK	Envelope glycoprotein H (PDBID:4XHJ)	-725.94
			Thymidine kinase (PDBID: 1OSN)	-967.51
			Protease (PDBID:1VZ)	-611.60
7	Fv16	KKVGTSKVVAKTVTKK	Envelope glycoprotein H (PDBID:4XHJ)	-582.14
			Thymidine kinase (PDBID: 1OSN)	-882.43
8	AVP 1074	RRKKAAVALLPAVLLA	Thymidine kinase (PDBID: 1OSN)	-848.62
			Protease (PDBID:1VZ)	-605.48
9	Magainin 1	GIGKFLHSAGKFGKAFVGEIMKS	Thymidine kinase (PDBID: 1OSN)	-840.59
			Protease (PDBID:1VZV)	-617.97
10	Dahlein 5.6	GLLASLGKVFGGYLAEKLKPK	Thymidine kinase (PDBID: 1OSN)	-803.63
11	GLK-19	GLKKLLGKLLKKLGKLLLK	Envelope glycoprotein H (PDBID:4XHJ)	-589.28
			Thymidine kinase (PDBID: 1OSN)	-883.56

4. Discussion

This research focused on using new computerized methods which involved studying affinity of the peptides to bind to specific receptor sites of varicella zoster virus by a specific computerized program (hex 8.0.).

A number of the selected peptides binds with the three varicella zoster virus (VZV) targets (envelope glycoprotein H, thymidine kinase, and protease) to know the interaction between targets and peptides using a process called molecular docking, so molecular docking is a widely used computer simulation procedure to predict the conformation of a receptor-ligand complex where the receptor is usually a protein or nucleic acid molecules and the ligand is either a small molecules or other proteins, and in this study the receptor is part of VZV (envelope glycoprotein H), and VZV enzymes (thymidine kinase and protease) as target while the ligand is a peptides, these peptides were selected because of their relatively low molecular weight, lesser toxicity, rapid elimination from the host, lesser side effects and cost effective.

After docking the ligand-receptor complex will form the expected output is docking energy. Among the different peptides, the best one can be selected based upon the lowest energy value which is an indicated of the highest stability (high negativity shows good binding to VZV target, so high negativity mean low energy so this will lead to high stability).

In the current study, several tests were done, to know the properties of the peptides then choose the best peptides that fit with VZV target and have the preferred properties. The first one is the cell penetration peptide (cpp) test; this test gives us an idea about the ability of the peptide for penetration into the cell membrane because of the VZV an intracellular virus so we need peptides that can enter into the cell to work on it, so this test is very important. If the cpp score is negative, this means the peptide is non-cell penetrating and if the cpp score is positive the peptide is cell penetrating, and it is ability to enter into the cell increase when the valve increase. Furthermore, the classI immunogenicity test was done, this test indicates the possibility of the reaction between the selected peptides and the immune system if the score of this test was positive this mean the immune reaction occur while the negative score mean there is no reaction. In addition to that, the toxicity test was done, this test suggests the possibility of the antimicrobial peptide either be toxic or not so, selection of the peptides must be carefully done to ensure that it isn't toxic. On the other hand, Boman index test was performed, this test shows the ability of the peptides to bind to other proteins rather than the protein targets, so if the Boman index value was high this mean the peptide has multifunction while if the E-value is low, this means there was a limited side effect. On the other hand, the hydropathicity test suggested the peptides will be dissolved in water or not. If the E-value is positive this mean it is insoluble in water while if it is negative this mean it is soluble

in water and the hydropathicity value of this peptide must be not very high or very low and be between them, in addition to that the molecular weight test was done, if the molecular weight of the peptides was low the properties will be better because of the adverse immune response is low so the efficacy will be better. After these tests were done, there is only eleven peptides meet the desired properties.

As shown in Table 6, from 64 peptides only 6 peptides are selected to be most appropriate to fit with the (envelope glycoprotein H) target and without the problem of cell penetration, immunogenicity, and toxicity. So these 6 peptides may be predicted as anti-VZV in the future. From the dimensional structure of the peptide with the target (as shown in Table 7) nearly the six peptides binding to their target in the same position.

The MSI-78 which has the highest E-value (-791.09 Kcal/mol), so it was indicated high binding affinity with the target, it was demonstrated broad spectrum in vitro antimicrobial activity against most of the common pathogens intact directly on the anionic phospholipid of the bacteria cell membrane which called lipopolysaccharide (LPC), so its mechanism based on the disruption of the bacterial membrane permeability barrier which in turn lead to loss of membrane integrity & ultimately to cell death [36].

Peptide A was the second highest E-value (-725.94 Kcal/mol) and Boman index value (2.29), in addition to that has the highest cpp test value (0.51), and both of these properties may enhance the theoretically estimated multi-functionality, due to the fact that the major fraction of protein is located inside the cell and bacterial membranes contain phospholipids with or without carbohydrate chains as the bulk material. As the binding of peptides to bacterial membranes involves the lipids rather than proteins, the index should be unrelated to the bactericidal effects of the peptides [35].

While polyphemusin, has good E-value (-597.55 Kcal/mol) and highest Boman index value (3.75) as compared with the others, so we expected this high value may be good and bad at the same time, it is good because the peptide may work on more than one protein sides and bad since it work on more sides so this may result in more adverse effects than other peptides. It was a cationic peptide CAP-derived from the horseshoe crab -Limulus polyphemus. These CAPs have been shown to be active in vitro against bacteria, fungi and even viruses, including vesicular stomatitis virus, influenza A virus, and human immunodeficiency virus (HIV-1). polyphemusins have also a pronounced activity against yeast and a lower activity against phylamentous fungi, also it can be predicted to be as anti-VZV [37].

K4-S4 (1–16) is potent to inhibit N. gonorrhoeae, it could be very useful in a variety of antimicrobial applications, especially against opportunistic fungal infections such as Candida, which is the most commonly encountered fungal pathogen in the human vagina. Since it has low molecular weight (1583.25 Dalton), so this mean it has a less predicted immuno-

genic reaction [38].

The peptide GLK-19 was found to be active against Gram-negative E. coli but not Gram-positive Staphylococcus aureus. But the results showed that the GLK-19 has a good binding and stability with the targets, the E-value was (-589.28 Kcal/mol) [39].

The FV16 peptide is a molecule with antiviral activity [5]. Due to limited researches concerning this molecule, and the scope of its action against the numerous virus targets still in need to be evaluated, this is done using another bioinformatics approach, the molecular docking. This peptide has the lowest E-value (-582.14 Kcal/mol) and cpp test value (0.02), so from this, it can be expected that this peptide having the lowest binding ability with the target than other peptides.

In another hand, from 64 peptides only 11 peptides are selected to be most appropriate to fit with the (Thymidine kinase) target and these have good cell penetration, immunogenicity, and toxicity properties, so these 11 peptides are predicted to be anti-VZV. From the three-dimensional structure of the peptide with the target the eleven peptides binding with their target in two different positions (five of them bind nearly to the same position and the remainder binds to the other position).

Magainins was found to be the best E-value (-840.59 Kcal/mol) with low Boman index value (0.08) as compared with the other peptides, so this low value may indicate that this peptide has limited adverse effects. This peptide is also known as PGS (peptide glycine-serine) [33], are 23 amino acid long peptides isolated from the skin of the African clawed frog Xenopuslaevis [34]. Magainins belong to a large family of amphibian amphipathic α-helicalantimicrobial peptides. Those peptides previously indicated to be characterized by a wide spectrum of antimicrobial activities. These were against Gram positive and Gram negative bacteria in addition to the fungi. In another hand, some researches indicated that the magainins have antiviral properties. For example, magainins-I exhibited inhibited Herpes Simplex Virus-1 and 2 [40].

Peptide F also has cell penetration possibility with its Boman index (equals 1.19). These results suggest that this peptide is oligo-functional. In addition, peptides A and F subjected to DNA binding inside microbial cells, this may expand their multi-functionality.

In another hand, Dahlein 5.6 peptide has the lowest E-value (-803.68 Kcal/mol), cpp test value (0.05) and Boman index value (-0.3), so this will indicate that this peptide has a low binding affinity to the target, also it is penetrating into the cell was little and has limited adverse effects. It is one member of Amphibian peptides, the dahlein 5.6 are amongst the most active neuronal nitric oxide synthase NOS inhibitors so far isolated from amphibians, and the NOS inhibit the formation of nitric oxide (NO). The NO is an anti-microbial agent.

Fur the rmore MSI-78, A, GLK-19, Fv16, Polyphemusin 2, AVP 1092 AVP 1074 and K4S4(1-16) all these peptides have high binding affinity, and the E-value for them were

-1027.32, -967.51, -883.56, -882.43, -876.07, -827.8, -848.62 and -860.48 respectively. The MSI-78 has a higher binding affinity due to its energy was the lowest one of these selected peptides but has the larger molecular weight among these peptides but it still weak immunogenic character which may reduce adverse immune response that eliminated peptides efficiency.

Finally, the last target was 1VZV- Protease it's docking values with the selection peptide. Only fifth peptides from 64 peptides suggested to be anti-VZV peptides they include MSI-78, K4S4 (1-16) a, Magainin 1, A and AVP 1074. The five peptides show a good binding their E-values are -643, -632.87- 617.97, -611.60 and -605.48 Kcal/mol respectively.

The best binding affinity wit0h these three targets was MSI-78, it shows the lowest energy among these peptides.

Some of these eleven peptides can bind with more than one targets, with K4S4(1-16)a, MSI-78, and A peptides, these three peptides can bind with the three targets, so this will indicate that their ability to act as anti- vzv drugs in the future was high, while Polyphemusin 2, Fv16, AVP 1074, Magainin 1, and GLK-19 peptides, all of these peptides can bind with two of the targets and this will be considered a good property for these peptides, on the other hand, the F, AVP 1092, and Dahlein 5.6 peptides act only on one target.

In conclusion, Since the antimicrobial peptides included Polyphemusin 2, K4S4(1-16) a, F, AVP1092, MSI-78, A, Fv16, GLK-19, Magainin 1, and Dahlen 5.6 bond with VZV targets with acceptable physical and chemical properites, so they may have the ability to inhibit VZV and may have the potential to work as promising inhibitors for VZV in the future.

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