Docking Analysis of Derivatives of Moronic Acid and Betulonic Acid against Oral Herpes Simplex Type-1

Ginni Singh, Abheek Chaudhuri
Department of Bioinformatics, University Institute of Engineering & TechnologyChhatrapati Shahu Ji Maharaj University, Kanpur-208024, Uttar Pradesh, India

Corresponding author
Ginni Singh
Department of Bioinformatics, University Institute of Engineering & TechnologyChhatrapati Shahu Ji Maharaj University, Kanpur-208024, Uttar Pradesh, India

Abstract

Herpes simplex (HSV-1) is also commonly referred to as cold sores, fever blisters. It is a viral infection of the skin that may occur once or return again and again.Herpes simplex begins as a group of small red bumps that blister and proceeded by itching and burning of the area.The crust then falls off and the redness slowly goes away. The whole process takes about 10-14 days.The protein 16VP is responsible for causing the oral herpes simplex type-1. 16VP is also known as also known as Vmw65 or αTIF(Trans inducing factor) is a trans-acting protein that forms complex with the host transcription factors Oct-1 and HCF to induce immediate early gene transcription in the herpes simplex viruses.MORONIC ACID and BETULONIC ACID are the natural compounds which can be used against 16VP protein. This work has been reported the docking study of prescribed drugs for Herpes simplex type-1 i.e., Moronic acid and Betulonic acid from Drug bank their derivatives for 16VP protein. Than docked energy have been scored to identify structurally active lead compound that make similar interaction to those of bound complex of 16VP. .After result analysis it has been found that docked energy score of Moronic acid and Betulonic acid derivatives [ACILAKJN, 3B-O-ISOVALERORYL-MORONIC ACID] HAS-143.796 kcal/mol which is better than in comparison to 16VP docked to original drugs. This derivative docked into effecter region forming interaction with amino acids. This derivative has been also following the Lipinski 5 rules and ADME properties. So in future this derivative can be serving as an effective drug to inhibit function of 16VP protein, which will in turn arrest the process of Herpes Simplex type-1.

KEYWORDS:HSV,16VP, αTIF, Oct-1, HCF, ADME

Introduction: Cold sores are caused by a virus called herpes (pronounced hur-peez). Herpes outbreaks are one of the most common viral infections in the world. The medical name for the specific virus that causes cold sores is Herpes Simplex. Herpes simplex (HSV-1) is also commonly referred to as cold sores, fever blisters, oral herpes or herpes labialis. It is a viral infection of the skin that may occur once or return again and again. This happens when the virus is cleared from the skin by the immune system it hides in the nerves and is never completely removed from the body.

Herpes outbreak infections are very common. It is estimated that nine out of ten people have been exposed to herpes outbreaks and many of these don't even know they have it. Those who carry herpes can spread the disease without even knowing it. Herpes simplex begins as a group of small red bumps that blister and preceded by itching and burning of the area. The blisters begin to dry up after a few days and form a yellow crust. The crust then falls off and the redness slowly goes away. The whole process takes about 10-14 days. Scars rarely form.

Herpes simplex virus (HSV) is a large double-stranded DNA virus, which is transcribed and replicated in the host cell nucleus. During infection, the viral genes are coordinately expressed in three phases immediate early (IE) or a, delayed-early or b, and late or g. This cascade of viral gene expression is initiated by an HSV virion protein called VP16 (also called aTIF, Vmw65, or VF65)

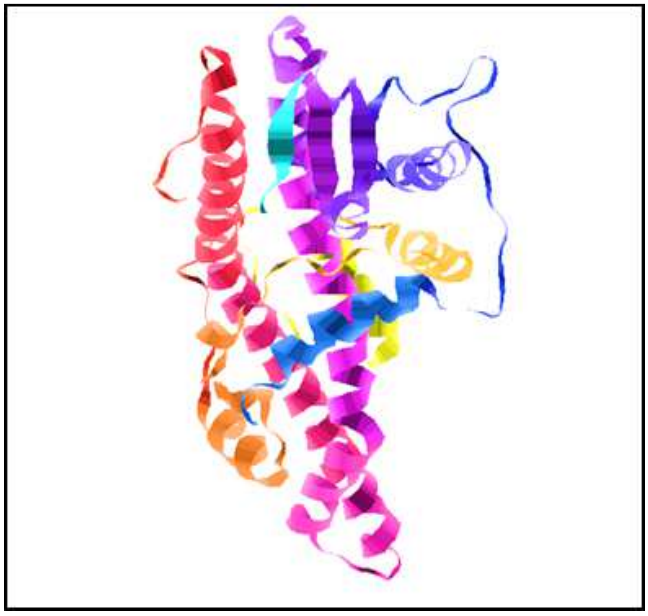

Fig No: 1 Protein 16VP.

- Number of chains: - 4.
- Number of groups: - 311.
- Number of atoms: - 2527.
- Number of bonds: - 2529.

Fig No: 2 Binding site prediction.

- MORONIC ACID and BETULONIC ACID are the natural compounds which can be used against 16VP protein.

KEGG PATHWAY OF HSV-1

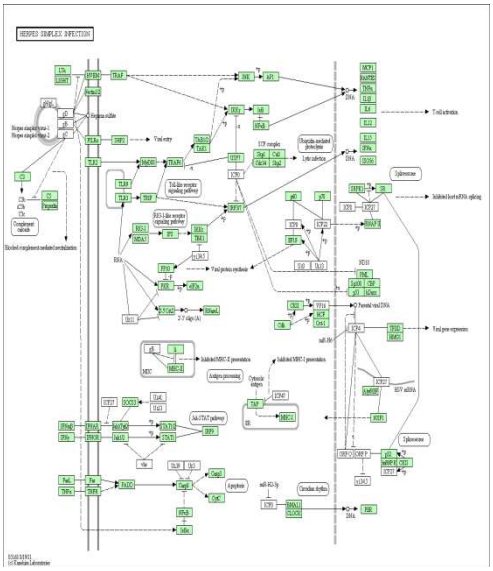

Fig No: 3 PATHWAY OF HSV-1.

METHEDOLOGY

1. Search information about oral herpes simplex type-1 in literature

2. Download the PDB file from RCSB PDB
3. Visualize the structure of 16VP with the help of pymol.
4. See the Binding site of 16VP with the help of Q-site finder.
5. Natural compound in literature that suppress the activity of 16VP
6. Design the Derivatives of Moronic acid and Betulonic acid.
7. Docking perform by using molegro virtual screening.
8. Select the best inhibitors among all.
9. Find out the analogs of best dock inhibitors by performing virtual screening.

MATERIAL

DATABASES

PubMed (z)

PubMed Central is a free digital database of full-text scientific literature in biomedical and life sciences. It grew from the online Entrez PubMedbiomedical literature search system. PubMed Central was developed by the U.S. National Library of Medicine (NLM) as an online archive of biomedical journal articles. Here, it has been used for searching the corresponding literature regarding the project.

NCBI

Established in 1988as a national resource for molecular biology information, NCBI creates public databases, conducts research in computational biology develops software tools for analyzing genome data and disseminates biomedical information all for the better understanding of molecular process affecting human health and disease. NCBI sequence database research accepts genome data sequencing projects from around the world and serve as an important tool for bioinformatics. Here, NCBI is used for retrieving the human D2 receptor is form.

Drug Bank

The drug database is a unique bioinformatics and chemo informatics resource that combines detailed drug (chemical, pharmacological, pharmaceutical) data with comprehensive drug target (Sequence, structure and pathway) information. The database contains nearly 4800 drug entries including > 1350 FDA approved small molecule drugs, 123 FDA approved biotech drugs, 71 neutaceuticals drugs and > 243 experimental drugs. Here, the drug bank is used for retrieving the 3D structure and its corresponding information.

ChemSpider

ChemSpider is a free chemical structure database providing fast text and structure search access to over 26 million structures from hundreds of data sources.

SOFTWARES

PyMol

PyMol is an open source, user-sponsored, molecular visualization system created by Warren Lyford Delano and commercialized by Delano scientific LLC, which is private software company dedicated to created useful tools that become universally accessible to scientific and educational communities. The "Py" portion of the software's name refers to the Python Programming Language. It is the open source visualization tool for use in structural biology.

Marvin Sketch

Marvin Sketch is an advanced chemical editor for drawing chemical structures, queries and reactions.Marvin Sketch allows users to quickly draw molecules through basic functions on the GUI and advanced functionalities such as sprout drawing, customizable shortcuts, abbreviated groups, default and user defined templates and context sensitive popup menus. Marvin Sketch has a rich support for atom and bond properties.Users can assign stereochemistry, charge, valence, radicals and isotopes to each atom. Single, double, triple bonds and aromatic forms are supported. Moreover using wedge bonds user can assign stereochemistry to atoms. Additional data fields can also be attached to atoms; via "S-group" logic so that any user defined information can be stored directly with the structural information.

DiscoveryStudio

Discovery Studio is a protein modelling program that contains tools to visualize, analyse, modify and simulate protein structures. Discovery Studio is a client-server software suite, built on the Pipeline Pilot visual programming product from Accelrys and can be run on both Microsoft Windows clients and servers and also Red Hat and Suse Linux clients and servers. The product suite includes both paid-for licensed versions and free visualization client tools. The product suite has a strong academic collaboration programme, supporting scientific research and makes use of a number of software algorithms developed originally in the scientific community, including CHARMM, MODELLER, DELPHI, ZDOCK, and DMol3and more.

Here it has been used for naming the ligands so that it makes the result interpretation easy by identifying with its specific name.

Molegro Virtual Docker

Molegro Virtual Docker is an integrated platform for predicting protein - ligand interactions. Molegro Virtual Docker handles all aspects of the docking process from preparation of the molecules to determination of the potential binding sites of the target protein, and prediction of the binding modes of the ligands.

LIPINSKY'SFILTER

Lipinski's rule of 5 helps in distinguishing between drug like and non-drug like molecules. It predicts high probability of success or failure due to drug likeness for molecules complying with 2 or more of the following rules:

- Molecular weight less than 500 Dalton.
- Less than or equal to 10 hydrogen bond acceptor.
- Less than or equal to 5 hydrogen bond donor.
- LogP value less than 5.

RESULT AND DISCUSSION

Docking view of a protein 16VP which is responsible for causing HSV Type-1.

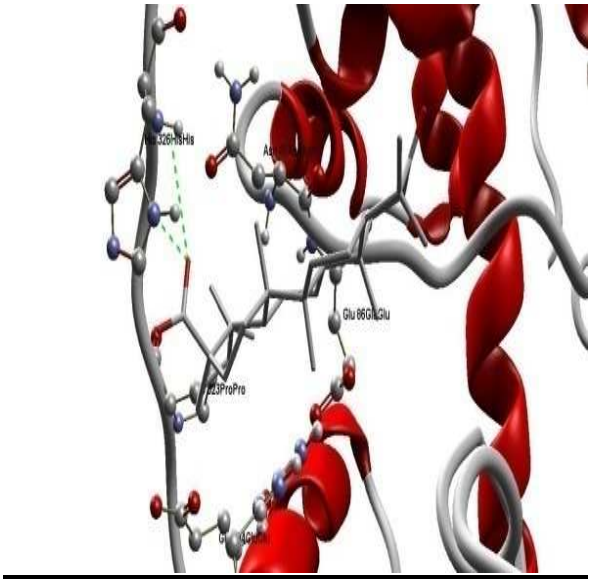

Fig No: 4 Docking view of a natural compound (Betulonic acid and Moronic acid) which suppress the activity of 16VP.
Amino Acids Involved in Hydrogen Bond Interactions is Pro 93, Ala 91, Ser262, and Asn 95.

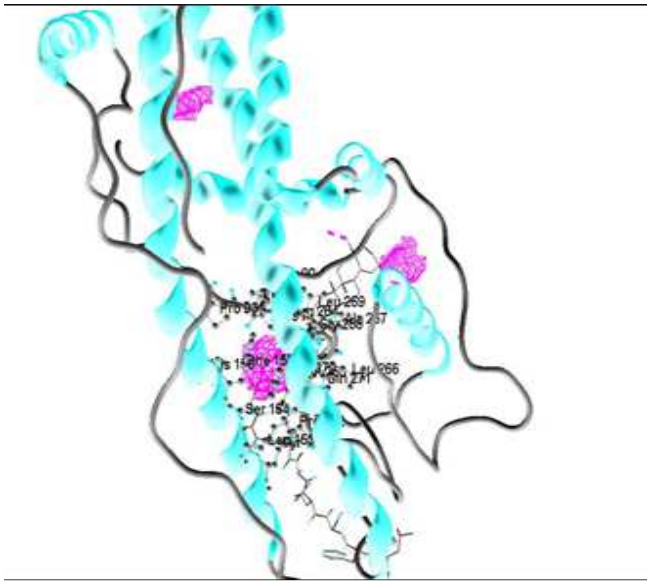

Fig No: 5 Docking view of a natural compound

Docking view of a best 5 inhibitors

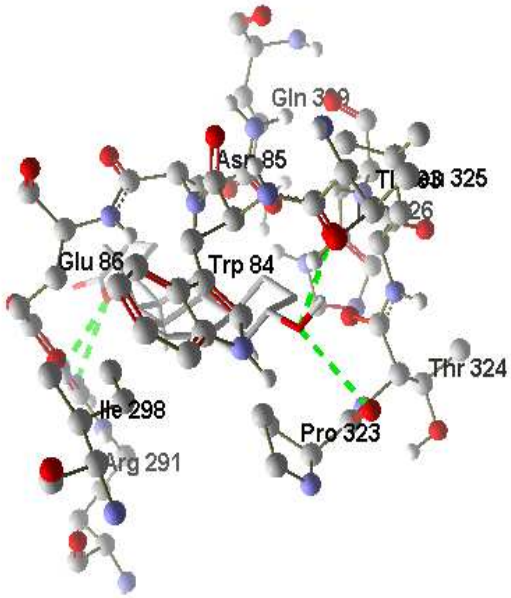

Fig No: 6 3B-O-ISOVALERORYL-MORONIC ACIDS
Amino Acids Involved in Hydrogen Bond Interactions is Pro 323, Trp 84, Glu 86.

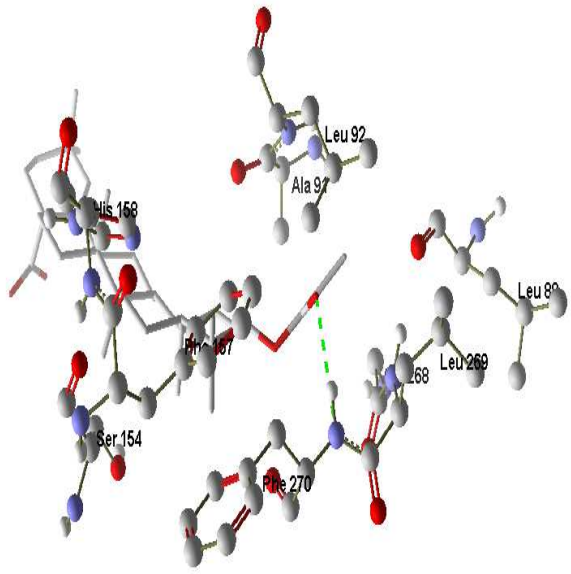

Fig No: 7 AMINOPTERINE
Amino Acids Involved in Hydrogen Bond Interactions isPhe 270, Phe 167.

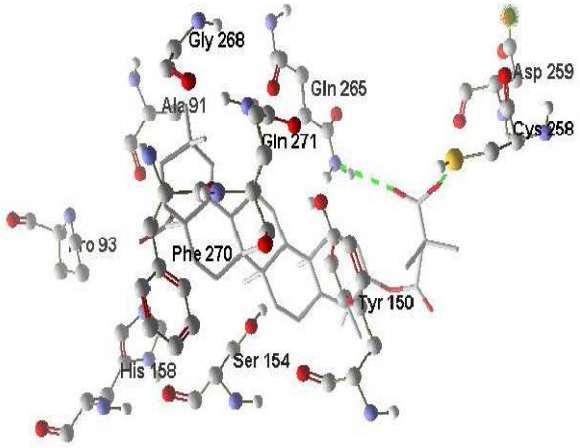

Fig No: 8AC1LAKJN
Amino Acids Involved in Hydrogen Bond Interactions

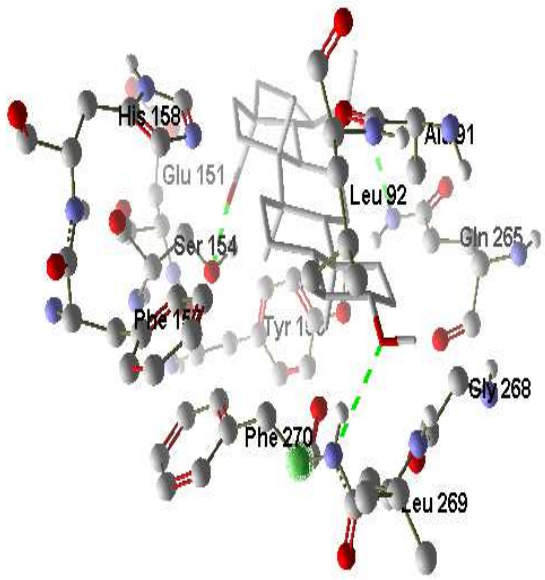

Fig No:9 METHOTREXATE

Amino Acids Involved in Hydrogen Bond Interactions arePhe 270, Leu 269, Leu92, Ser 154, Ala 91.

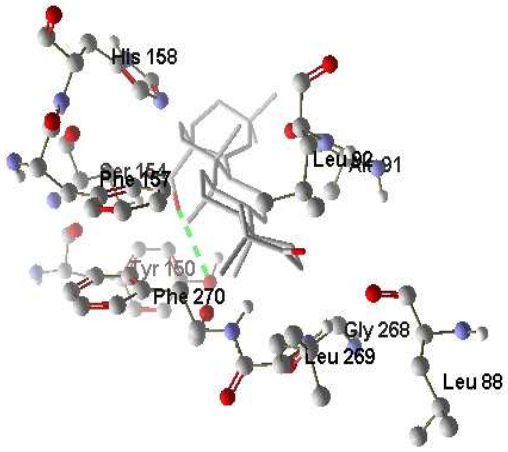

Fig No: 10 3B-O-VALERORYL-MORONIC ACIDS

Amino Acids Involved in Hydrogen Bond Interactions isPhe 270, Phe 157

DOCKING RESULT

S.NO	LIGAND NAME	MOLDOCK SCORE	H BOND
1.	3B-O-Betyryl-moronic acid	-98.0924	-1.38532
2.	3B-O-Isobutyryl-moronic acid	-82.053	-5.67046
3.	3B-O-Isovaleroryl-moronic acid	-107.659	-5
4.	3B-O-Propionyl-moronic acid	-82.3772	-6.00153
5.	3B-O-Valeroryl-moronic acid	-102.74	-5.641
6.	3-nitropropionic acid	-59.3998	-12.5356
7.	ACILAKJN	-106.696	-12.4994
8.	Aminopterin	-124.205	-20.3763
9.	Bis (p-chlorophenyl) acetic acid	-90.9454	-11.5322
10.	dihydrobetune	-15.1094	0.657788
11.	Etodolac	-96.4335	-12.4245
12.	Ferulic acid	-77.7957	-6.22655
13.	Foscarnet	-52.8208	-19.5544
14.	Gamma-Aminobutyric acid	-54.0073	-5.95552
15.	Indomethcin	-77.1687	-3.19963
16.	Methotrexate	-121.287	-18.7306
17.	Moronic acid	-28.0361	-5
18.	Nialamide	-76.0054	-6.64974
19.	Phosponoacetic acid	-72.949	-17.8006
20.	Ticrynafen	-91.7959	-5.83815
21.	Tryptophan	-90.4427	-9.97259
22.	Vaoroic acid	-74.1616	-7.59217
23.	Vigabatrin	-66.6885	-8.0968

TABLE NO: 1**Ligand names along with their moldock score and H-bond interaction with the receptor.**

S.NO	LIGAND NAME	MOLDOCK	H.BOND
1.	Aminopterine	-124.205	-20.3763
2.	Methotrexate	-121.287	-18.7306
3.	3B-O-Isovaleroryl-moronic acid	-107.659	-5
4.	AC1LAKJN	-106.696	-12.4994
5.	3B-O-Valeroryl-moronic acid	-102.74	-20.3763

TABLE NO: 2 **Best 5 result of docking of inhibitors.**

Analogs of best 5 inhibitors found by ZINC DATABASE and finally do virtual screening.

- AMINOPTERIN.
- METHOTREXATE.
- 3B-O-ISOVALERORYL-MORONIC ACID.
- AC1LAKJN.
- 3B-O-VALERORYL-MORONIC ACID.

Analogs of 5 best inhibitors.

S.NO	LIGAND NAME	MOLDOCK	H BOND
1.	ZINC02036915	-110.989	-14.7482
2.	ZINC18847072	-104.314	-16.4008
3.	ZINC01529323	-122.247	-9.09507
4.	ZINC06920406	-108.352	-5.073947
5.	ZINC36378553	-119.418	-11.2338
6.	ZINC36378554	-122.316	-11.7865
7.	ZINC22062144	-98.3547	-10.6105
8.	ZINC22062147	-100.92	-7.24572
9.	ZINC08651759	-95.9556	-19.4406
10.	ZINC13284373	-118.127	-9.77111
11.	ZINC13284302	-130.554	-14.8151
12.	ZINC02944400	-104.564	-12.3036

TABLE NO: 3 **ANALOGS OF AMINOPTERINE**

S.NO	LIGAND NAME	MOLDOCK	H BOND
1.	ZINC06920406	-120.595	-16.0683
2.	ZINC01529323	-110.293	-14.0517
3.	ZINC02036915	-106.984	-8.22412
4.	ZINC18847072	-120.407	-12.0054
5.	ZINC36378554	-126.295	-10.957
6.	ZINC36378553	-122.873	-7.82071
7.	ZINC22062147	-93.818	-11.3685
8.	ZINC22062144	-95.2975	-13.0686
9.	ZINC08651759	-90.3201	-13.7713
10.	ZINC13284373	-121.72	-11.9754
11.	ZINC08655696	-115.199	-9.5328
12.	ZINC22060774	-115.199	-9.5328
13.	ZINC22060774	-115.199	-9.5328
14.	ZINC22060774	-113.906	-12.9353
15.	ZINC22060777	-113.906	-12.9353
16	ZINC22060777	-113.906	-12.9353

TABLE NO: 4 **ANALOGS OF METHOTERXATE**

S.NO	LIGAND NAME	MOLDOCK	H BOND
1.	ZINC71766902	-81.7594	-4.77249
2.	ZINC71766903	-77.2043	-3.81541
3.	ZINC71766904	-95.036	-2.5
4.	ZINC71766905	-82.993	-1.59935

TABLE NO: 5 **ANALOGS OF 3B-O-VALERORYL-MORONIC ACID**

ANALOGS OF AC1LAKJN

127 Analogs are present.

ANALOGS OF 3B-O-ISOVALERORYL-MORONIC ACID

308 analogs are present.

NOW WE COLLECT THE BEST 5 ANALOGS AND PERFORM A VIRTUAL DOCKING.

S.NO	LIGAND NAME	MOLDOCK	H BOND
1	ZINCO2036915	-135	-18.6981
2.	ZINCO6920406	-143.796	-14.6992
3.	ZINCO8655696	-137.696	-14.1026
4.	ZINC22060777	-132.369	-10.7742
5.	ZINC22062147	-138.833	-14.2288
6.	ZINC34871028	-130.579	-10.9316
7.	ZINC36378554	-135.206	-12.2831
8.	ZINC37629395	-130.346	-3.27114
9.	ZINC70665353	-130.298	-2.5
10.	ZINC70698515	-131.84	-2.5

TABLE NO: 6**AFTER VIRTUAL SCREENING BEST REULT OF 10 INHIBITORS.**

CONCLUSION

Among all best 5 inhibitors (AC1LAKJN, 3B-O-ISOVALERORYL-MORONIC ACID) are showing best docking score to find the similar molecules from zinc database.

After result analysis it has been found that docked energy score of Moronic acid and Betulonic acid derivatives [ACILAKJN, 3B-O-ISOVALERORYL-MORONIC ACID] has-143.796 kcal/mol which is better than in comparison to VP16 docked to original drugs.

So in future this derivative can be serving as an effective drug to inhibit function of VP16 protein, which will in turn arrest the process of Herpes Simplex type-1.

ACKNOWLEDGEMENT

The authors wish to thanks Er. Brijendra Singh, from Department of Bioinformatics, University Institute of Engineering & Technology Chhatrapati Shahu Ji Maharaj University Kanpur for critically examining the manuscript and giving me valuable guidance related to Drug Designing.

REFERENCES

- Hernot S., Klibanov A.L., Microbubbles in ultrasound-triggered drug and gene delivery. ,Adv Drug Deliv Rev (2008).
- Lafferty W.E., Coombs R.W., Benedetti J., et al. Recurrences after oral and genital herpes simplex virus infection: influence of anatomic site and viral type.NEngl J Med ,316:1444–9 (1987)
- Mertz G., Genital herpes simplex virus infections. Med Clin North Am74:1433–54 (1990).

- Reske A., Pollara G., Krummenacher C., Chain B.M., Katz D.R., Understanding HSV-1 entry glycoproteins. Rev Med Virol(2007).
- Spear P.G., Manoj S., Yoon M., Jogger C.R., Zago A., Myscofski D., Different receptors binding to distinct interfaces on herpes simplex virus gD can trigger events leading to cell fusion and viral entry. Virology (2006).
- Knipe D., Howley P., Chanock R., Melnick J., Monath T., Whitley R. Herpes simplex virus. In: Fields B, et al, eds. Fields' virology. 3rd ed. Philadelphia:Lippincott-Raven, (1996).
- C.I.Ace, Dalrymple M.A., Ramsay F.H., Preston V.G., and Preston C.M, Mutational analysis of the herpes simplex virus type 1 trans-inducing factor, Vmw65. J. Gen. Virol,**69:** 2595–2605, (1988).
- Carpenter D.E. and Misra V., Sequences of the bovine herpesvirus 1 homologue of herpes simplex virus a-transinducing factor (UL48), Gene **119:** 259–263,(1992).
- Cousens D.J., Greaves R., Goding C.R., and Hare P. O',The C-terminal 79 amino acids of the herpes simplex virus regulatory protein, Vmw65, efficiently activate transcription
  in yeast andmammalian cells in chimeric DNA-binding proteins.
  EMBO J. **8:** 2337–2342 (. 1989).
- Dalrymple M.A., McGeoch D.J., Davison A.J., and Preston C.M., DNA sequence of the herpes simplex virus type 1 gene whose product is responsible for transcriptional activation of immediate early promoters. Nucleic Ac
- ids Res., (1985).