



# MOLECULAR DOCKING OF SELECTED BIOACTIVE COMPOUNDS FROM GLYCYRRHIZA GLABRA

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**ABSTRACT:** In this study glycyrrhizic acid derivatives has been taken, since Glycyrrhiza glabra has excellent antiviral activity and has been used since ancient times. An instantaneously qualifying technique is utilized to discover a natural antiviral medicine that will be helpful in the treatment of various viral infections as well as the prevention of several pandemic diseases SARS-COVID 19 and influenza A/H1N1. For molecular docking study main targeting protease (Pdb id: 6i3h) is gaining importance in designing of antiviral drug active against H1N1. An attempt has been made to suggest an in silico computational relationship between glycyrrhizic acid derivative and an influenza protein 6i3h. The docking score were calculated by glide based docking and best docking score found with some of the glycyrrhizic acid analogues.

**KEY WORD:** GL, 6I3H, H1N1, GA, HPLC, 2D and 3D, CD, Å

## INTRODUCTION

Due to the widespread distribution of viral infections that are socially dangerous, such as HIV, hepatitis B and C, and the emergence of new viral infections, such as "avian flu" and "swine flu," influenza A/H1N1, Ebola fever, etc., the search for new antiviral agents is one of the most crucial tasks in chemistry and medicine. The World Health Organization (WHO) declared the pandemic influenza caused by a new strain of H1N1, which was identified as influenza virus formed as a result of a triple assortment swine, avian, and human viruses and called influenza A/H1N1pdm09, to be the cause of 162,380 cases and 1154 deaths in 168 countries as of April 2009 [1]. There are two types of influenza A virus among the most virulent ones to have ever been discovered, and it has been responsible for multiple major pandemics. [2] Due to their effective performance in clinics and as alternative remedies for various ailments, low-toxicity,

natural materials are increasingly being used for treatment of many severe conditions.

Many antiviral drugs derived from natural herbs, mostly those from China, **glycyrrhizic acid** is the example of these types of drug and showed pharmacological activities like antiviral, anti-allergic, antimicrobial, anticancer, antioxidant, hypolipidemic, cardiovascular, central nervous, respiratory, immunological, anti-inflammatory, analgesics, antipyretic etc. [14] Glycyrrhizic acid is a triterpenoid and isolated from

glycyrrhiza glabra l. and Gl. Uralensis Fisher roots, stolons of perennial plants belonging to the legume family where glycyrrhizic acid (GA), a natural sweetener that is widely used in cosmetics and pharmaceuticals, is separated. It has a sweetness corresponding to a distinctive licorice flavour, frequently referred as "cooling." With no caloric value and around 50 times the sweetness of the taste of sucrose is sluggish to start and tends to longer. [10] One of the straightforward but beneficial method for assessing the potential of secondary metabolites as influenza virus antagonist are the molecular docking.

Molecular docking has a number of benefits over other in silico methods. In addition to being quick and not requiring a lot of resources, molecular docking offers an illustration of the relationship between ligands and receptors that cannot be acquired via any other method. [24] The main issue with docking is that the in vitro results are not always applicable when using affinity as the primary parameter of observation.

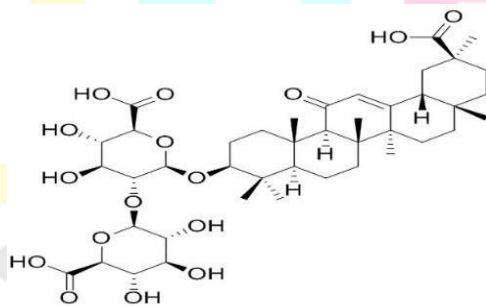
This study aimed to find activity of GA derivatives against H1N1 by molecular docking methods. Protein used in this study is 6I3H.

GL are the main plant-derived metabolites that are effective for the long-term treatment of HIV infection and also in long term chemotherapy of viral hepatitis B and C. [4,5] GA Glycyrrhizic acid (GA), GL are appealing because to their low toxicity (LD50: 5000 mg/kg) and capacity to induce the production of c-interferon in vitro and in vivo, respectively. However, GL has some side effects and is only effective as an antiviral drug in vivo at high dosages. Because of its structural resemblance to corticosteroids, it may have an impact on how water and salt are exchanged, enhance the retention of Na<sup>+</sup>, and lower K<sup>+</sup> in some patients.

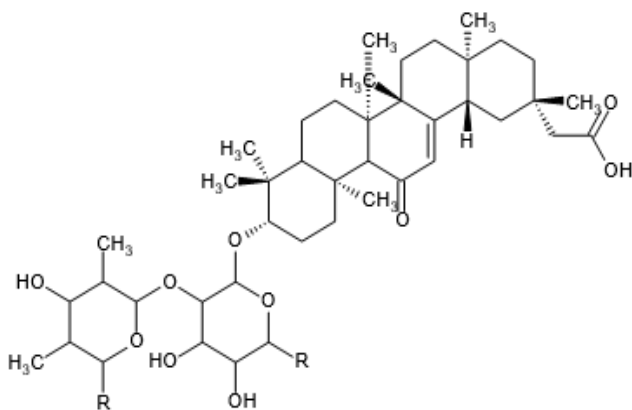
## METHODOLOGY:

Compounds derived from naturally occurring phytochemicals have demonstrated a number of recent development in contemporary clinical medicine in the treatment of resistant disorders.

**Ligand Preparation:** 19 compound of glycyrrhizic acid (**figure 1**) has been taken with their CD 50 values which was studied previously are active against influenza virus A and B. Structure were drawn by chem sketch and converted into 3D structures all structure are saved in .mol format, energy optimization, and ionization states are generated by (Force field batch energy optimization) Vlife MDS software. The 2D structure, all 19 compound are given below. complex bound to protein are removed along with water molecule and grid docking was performed with ligand for the detection.

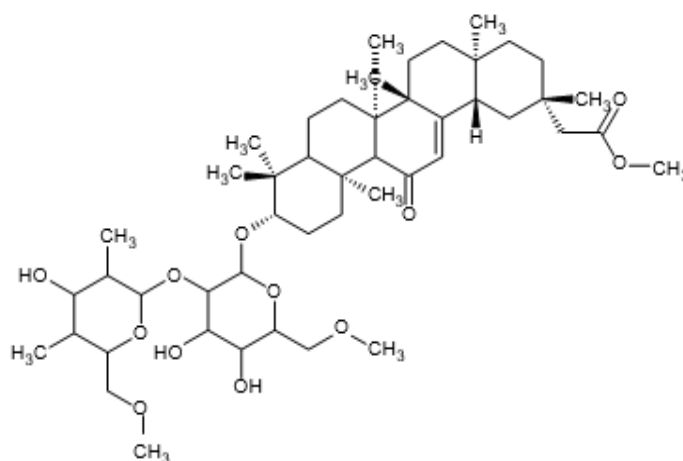
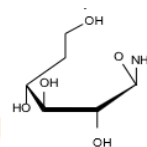


**Figure 1: Glycyrrhizic acid**

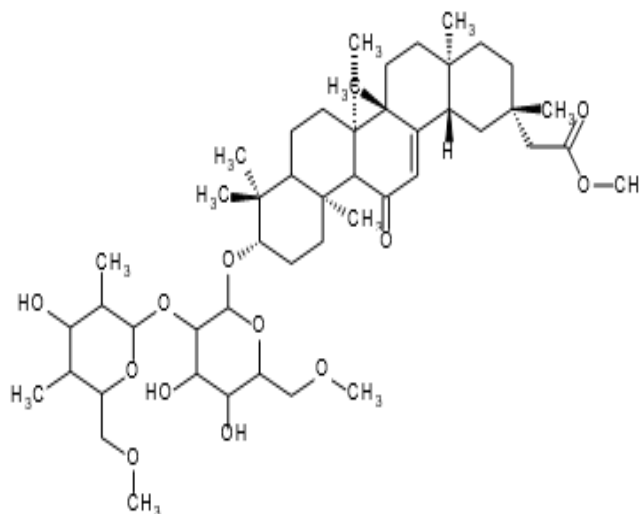


**Basic structure for 14, 15 & 16**

- |                            |                                 |                               |
|----------------------------|---------------------------------|-------------------------------|
| 1. R= R1 = OH              | 7. R= OH, R1=Val-<br>OMe        | 11. R= OH, R1= Lys<br>(Z)-OH  |
| 2. R= R1 = Phe-OMe         | 8. R= OH, R1= Hys-<br>OMe       | 12. R= OH, R1=<br>Lys(Z)-OBut |
| 3. R=R1 = Tyr-OMe          | 9. R= OH, R1 = Asp<br>(OMe)-OMe | 13. R = OH, R1 =<br>Lys(Z)-OH |
| 4. R=R1 = Ile-OMe          | 10. R = OH, R1 = Cys<br>(Bn)-OH | 14. R= COOH                   |
| 5. R= OH, R1 = Phe-<br>OMe |                                 | 15. R = CO Asp(OMe)-<br>OMe   |
| 6. R= OH, R1= Tyr-<br>OMe  |                                 |                               |
| 16. R = COAsp(OMe)- OH     | 17. R=OH, R1 =                  |                               |



(19)



(18)

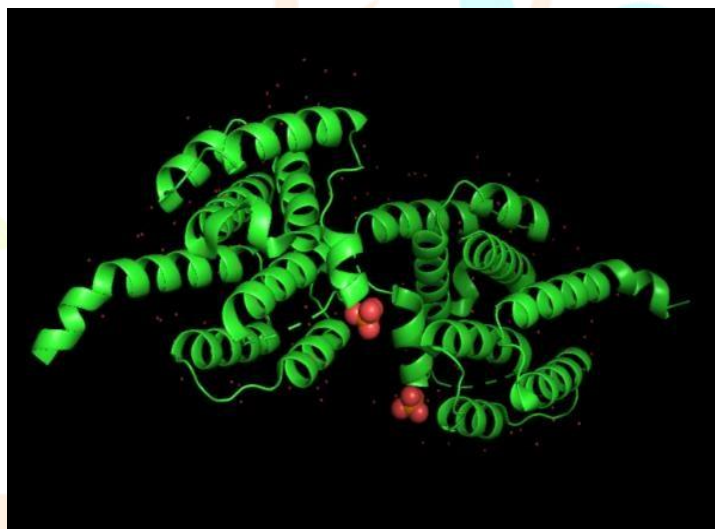


Figure 2: H1N1 protein (pdb id 6I3)

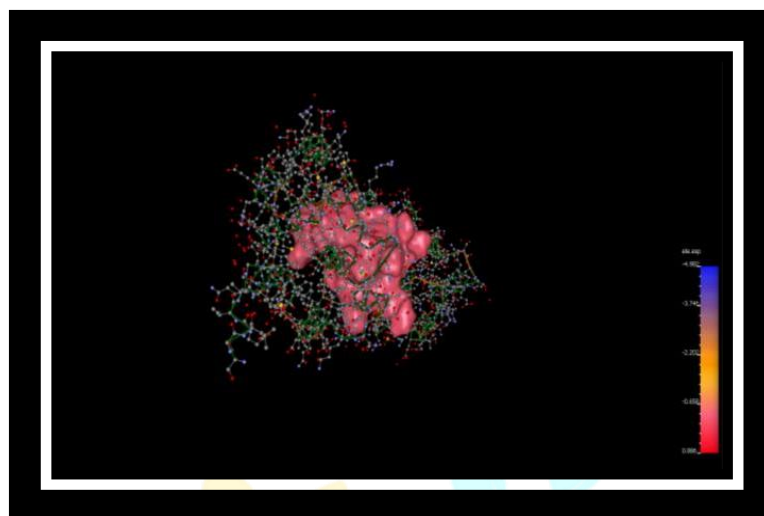
### Protein preparation for docking:

The X-ray diffraction based Crystal structure of influenza A virus M1 N-terminal domain (G18Amutation) with resolution of 1.90 Å selected for docking study of glycyrrhizic acid derivative (pdbid 6i3h) the protein structure (figure 2) downloaded from protein data bank and of shape and activity against H1N1.

### Docking Studies:

Molecular docking helps in studying drug/ligand or receptor/ protein interactions by identifying the suitable active sites in protein, obtaining the best geometry of ligand-receptor complex and calculating the energy of interaction for different ligands to design more effective ligands.

Initial screening was done by glycyrrhizic acid derivative with 6i3h protein by grid based batch docking using Vlifemds software, grid based batch docking is a type of rigid docking in which conformers are generated by selecting cavity#1 as a cavity in which ligand will be placed for docking (figure 3), The ligand which show best affinity toward protease will qualified, The interaction of selected ligand and protein docked complexes analyze and best ligand protein complex pose with their interactions are found.



**Figure 03: 6I3H protein showing Cavity #1**

**Result and discussion:** Pandemic influenza A/H1N1 2009 (pH1N1) virus was a considerable public health concern worldwide. Most infected people experienced mild and uncomplicated illnesses, but some patients developed rapidly progressive pneumonia that led to respiratory failure, shock, and death, as previously reported that the biological activity of GL might be increased by its chemical changes, and some semisynthetic GL derivatives were discovered to be effective immune modulators and antiviral agents against H1N1.

So we prepare many GL derivatives and 6I3h protease has been downloaded from the protein databank and prepared for further process by removing water molecule, adding charges etc.

Before starting molecular docking studies all drawn structures energies are optimized and are converted into 3D (**Table 01**):

**Grid based batch docking** is a rigid and exhaustive docking method, in this method after unique conformers are generated the receptor cavity of interest is chosen by the user and a grid is generated around the cavity (default grid interval size 1 Å).

From the biopredicta tool of vlifemds select docking then grid docking it provide option to select receptor, after selecting the receptor place ligand panel and choose the select cavity option cavity#1 click next to select ligand and start the batch docking the output window will report completion of docking process with minimum dock score, the list of all generated dock score is given in **table02**.

Out of 19 compounds evaluated from glycyrrhiza glabra the binding energies lesser than the upper threshold (-6Kcal/mol) were generally regarded as a cut-off in ligand binding studies, the binding affinity for protease 6I3H ranged between -3.135121 (**S01**) to -6.199069 (**S02**). The best binding affinity for protease 6I3H were found with S09, S15, S18, S19, values -5.903116, -5.519462, -5.970706, -6.199069 respectively. When comparing binding energies of S09, S15, S18 or S19 the best binding energy shown with S19.

**Figure 4** showed visualization of binding sites of bioactive compound from glycyrrhiza glabra to the active site of influenza protease 6I3H. The 3D and 2D visualization results clearly indicated that the ligand molecules bind to the active site of the influenza protease and therefore, it could be expected to inhibit the enzyme activity and stopped the replication of the virus



**Table 01: Difference in energies after optimization**

Code	Energy optimization	
	Before	After
S01	380.4267	342.3269
S02	657.8920	550.7970
S03	520.1387	477.1387
S04	483.3916	428.6315
S05	582.8073	435.9382
S06	840.743	434.1066
S07	966.255	335.0892
S08	598.228	329.345
S09	894.882	369.9081
S10	890.051	428.9853
S11	758.995	507.0405
S12	1114.791	427.1520
S13	1958.897	414.9236
S14	528.157	356.1119
S15	725.002	239.9558
S16	657.6439	433.5447
S17	575.7896	428.5328
S18	469.9845	263.4405
S19	390.6754	215.7760

**Table 02: Docking scores of ligands**

Compound name	Minimum Score
S01	-13.135121
S02	-12.982222
S03	-10.056120
S04	-7.203038
S05	-5.858810
S06	-6.058738
S07	-0.455685
S08	-10.306515
S09	-8.903116
S10	-8.530099
S11	-7.311790
S12	-10.509337
S13	-7.254801
S14	-6.233664
S15	-8.519462
S16	-10.227567
S17	0.168523
S18	-12.970706
S19	-6.199069

**Conclusion:** The use of natural drug for treatment, cure and prevention of disease is gaining attention due to long term effect and lesser side effect (GL) glycyrrhiza glabra is a common plant has been using from ancient time for the treatment of various disease, The present study proved that glycyrrhizic acid derivatives had antiviral activity against influenza H1N1. However, further in vitro and in vivo tests are required to assess the compounds from the tree as clinical drugs.

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