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Bridging *Ayurveda* and Bioinformatics: Unveiling the Antiviral Potential of Glycyrrhizic Acid Through Molecular Docking

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Abstract

Background: *Ayurveda* has a substantial collection of bioactive substances with potential therapeutic benefits, although their molecular processes frequently remain unexplored. Glycyrrhizic acid, a primary component of *Glycyrrhiza glabra* (Liquorice), was historically acknowledged for its antiviral characteristics. The integration of *Ayurvedic* expertise with bioinformatic techniques offers a novel method for the scientific validation of these substances. **Aim:** This study investigates the antiviral potential of Glycyrrhizic acid, a major bioactive constituent of *G. glabra* (Liquorice) widely employed in *Ayurvedic* medicine, through integrated computational and molecular docking analyses. **Method:** Molecular docking studies were performed against key viral targets, such as the Adenosine Triphosphate (ATP)-bound state of BiP (5E84), main protease (Mpro) (6LU7), spike receptor binding domain (6LZG), RNA-dependent RNA polymerase (6M71), spike glycoprotein (6VSB), NSP15 endonuclease (6VWW), Nsp9 RNA-binding protein (6W4B), papain like protease (6W9C), and neurominadase from H1N1 (5NZ4); which are involved in replication, proteolysis, and host-virus interactions were chosen because of their biological importance and structural availability in the Protein Data Bank. **Result:** Our results demonstrate that Glycyrrhizic acid exhibits superior binding affinity compared to the standard antiviral drug ribavirin, particularly against the spike receptor-binding domain (6LZG) with a docking score of -10.307 kcal/mol. These findings were confirmed by Molecular Mechanics/ Generalised Born Surface Area (MM-GBSA) calculations, which showed stable ligand-receptor complexes and advantageous binding free energy components. **Conclusion:** The potential of Glycyrrhizic acid as an antiviral drug is highlighted in this work, which also shows the value of combining contemporary bioinformatics techniques with *Ayurvedic* phytochemistry. The hypothesised antiviral pathways will be experimentally validated in future *in vitro* and *in vivo* research using the computational insights as a basis.

Major Findings: Molecular docking analysis revealed that Glycyrrhizic acid exhibits strong binding affinity with key viral target proteins, indicating significant antiviral potential.

Keywords: Drug Discovery, *Glycyrrhiza glabra*, MM-GBSA, Molecular Docking, Phytochemical, Virtual Screening

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1. Introduction

The emergence of respiratory influenza viruses, particularly SARS-CoV-1 and 2, has created urgent demand for effective antiviral therapeutics. Despite extensive research efforts worldwide, no definitive treatment has been established for these infections. Current scientific endeavours focus on discovering antiviral medicines through various approaches, including drug repurposing—examining existing pharmacological molecules for their potential as antiviral agents[1].

Computer-Aided Drug Discovery (CADD) tools have revolutionised the drug development process by enabling pharmaceutical corporations and research institutions to accelerate discovery while reducing costs and late-stage failures. Recent advances in robotics and high-throughput screening using microfluidic systems have further enhanced drug repurposing capabilities. Three primary computational drug repositioning approaches: network-based designs, structure-based methods, and Artificial Intelligence (AI) techniques are employed for discovering novel drug-target relationships[1,2].

Ayurvedic and *Siddha* traditional medicine systems, originating in India, include a class of herbs and preparations known as *Rasayana*, specifically designed to enhance the body's resistance. Scientific research has validated the unique properties of *Rasayana* plants, which show great potential in treating various ailments. Secondary metabolites derived from these plants can be effectively identified and utilised to treat infections[3].

Liquorice (*Glycyrrhiza glabra*) is considered a major *rasayana* drug in *Ayurvedic* medicine. Glycyrrhizic acid, one of its significant secondary metabolites, possesses multiple therapeutic properties, including lipid-lowering, antioxidant, antiviral, anti-inflammatory, and anticancer activities. Plants produce antiviral metabolites as secondary metabolites in response to viral infections. Since animal and plant viruses share similar structures, plant-derived secondary metabolites may effectively treat human viral diseases[4,5].

Previous research has demonstrated that compounds from traditional medicinal herbs possess antiviral effects. The novelty of this work lies in its multi-target docking approach, evaluating natural compounds across several essential viral proteins simultaneously, while also integrating ancient *Ayurvedic* knowledge with advanced bioinformatics to elucidate the molecular interactions of Glycyrrhizic acid and provide fresh insights into its antiviral mechanisms given the promising contribution of natural products to drug discovery, this study aims to assess the antiviral potential of Glycyrrhizic acid through *in silico* screening against nine different respiratory viral target proteins by employing molecular docking simulations and molecular dynamics studies.

2. Materials and Methods

2.1 Herbal Compound Retrieval and Drug Library Preparation

The 3D structure of Glycyrrhizic acid was retrieved from the PubChem database. Compounds lacking .mol/.sdf files were drawn and converted using the online Simplified Molecular Input Line Entry System (SMILES) translator and Structure File Generator. It is important to note that molecular docking relies on static protein–ligand structures, which may not fully reflect dynamic biological interactions and can limit the accuracy of predicted binding affinities and poses. Docking validation was performed by redocking each co-crystallised ligand into its native binding site and computing the Root Mean Square Deviation (RMSD) between the docked and crystallographic poses (RMSD ≤ 2.0 Å was used as the acceptance threshold). Proteins were prepared by removing crystallographic waters, adding polar hydrogens and appropriate charges, and saving as Protein Data Bank Partial Change and Atom Type (PDBQT; ligands were energy-minimised (MMFF94), assigned Gasteiger charges, converted to PDBQT, and treated as flexible during docking. Docking was carried out with AutoDock Vina (release v1.2.x), using a binding box centered on the co-crystallised ligand that encompassed the active site (box sizes typically ~20 × 20 × 20 Å, adjusted per target), exhaustiveness = 8–32 (increased to 32 for final rescoring), num_modes = 9–20, and energy_range = 3–4 kcal·mol^{-1}; best-scoring poses were visually inspected and ranked by binding affinity[6,7].

2.2 Target Protein Retrieval and Preparation

These nine viral targets were selected because each of them performs an essential function in the viral

life cycle, such as mediating host-cell entry, driving genome replication and transcription, processing viral proteins, or supporting viral assembly. They are also recognised as druggable proteins, meaning their active sites are suitable for binding small-molecule inhibitors. High-resolution 3D structures for all these proteins are available in the Protein Data Bank, which is necessary for reliable docking analysis. In addition, previous clinical or experimental studies have identified these proteins as important antiviral targets. Selecting targets that represent different stages and mechanisms of viral infection ensures a comprehensive evaluation and increases the chance of identifying meaningful interactions of Glycyrrhizic acid with multiple pathways involved in viral inhibition.

Based on a literature survey, nine major targets for studying antiviral activity against respiratory influenza viruses were identified:

- ATP-bound state of BiP (5E84)
- Main protease (Mpro) (6LU7)
- Spike receptor-binding domain (6LZG)
- RNA-dependent RNA polymerase (6M71)
- Spike glycoprotein (6VSB)
- NSP15 endonuclease (6VWW)
- Nsp9 RNA-binding protein (6W4B)
- Papain-like protease (6W9C)
- Neuraminidase from H1N1 (5NZ4)[8-12]

FASTA sequences were retrieved from the National Centre for Biotechnology Information (NCBI), and similar biological sequences were searched in the Protein Data Bank (PDB) using Basic Local Alignment Search Tool (BLAST). The top 5-10 Sequences were chosen according to the E-value, percentage identity, and query coverage. Three-dimensional X-ray crystallographic structures were obtained from the PDB databank and validated using variables such as co-crystal agonist, co-crystal ligand, and resolution, Ramachandran plot analysis[13,14] (Table 1).

Ramachandran plots were generated using the PROCHECK web tool to assess the three-dimensional geometry of protein models. The plots display regions energetically permitted for backbone dihedral angles ψ against φ of amino acid residues, categorised as favoured (red), additionally allowed (yellow), generously allowed (pale yellow), and disallowed (whitish yellow) regions[15,16].

With the University of California, San Francisco (UCSF) CHIMAERA v1.16, side chains were synthesised, and protein structures lacking residues were finished. Optimisation procedure was executed by applying one thousand iterations of the steepest Descent algorithm (step size 0.1 Å), succeeded with a total of 100 passes of the conjugate Gradient algorithm (step size 0.1 Å). Hydrogen atoms were added, protonation states assigned to histidine residues, and charges applied using Assisted Model Building with Energy Refinement (AMBER) ff14SB force field for conventional residues and Austin Model 1- Bond Charge Corrections (AM1-BCC) force field for unconventional residues. Proteins were purified by removing non-standard residues, water molecules, co-crystal ligands, and superfluous chains using Biovia Discovery Studio Visualiser V21.1.0.20298[17,18].

Table 1. Validation parameters for selected protein targets

Parameter	5E84	6LU7	6LZG	6M71	6VSB	6VWW	6W4B	6W9C	5NZ4	Standard
Method	X-ray Diffraction	X-ray Diffraction	X-ray Diffraction	X-ray Diffraction	X-ray Diffraction	X-ray Diffraction	X-ray Diffraction	X-ray Diffraction	X-ray Diffraction	-
Mutation	No	No	No	No	No	No	No	No	No	No
Resolution (Å)	2.99	2.16	2.50	2.90	3.46	2.20	2.95	2.70	1.36	~2.00
wwPDB Validation	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better
Rama chandran (Favored + Allowed)	89.8%	90.6%	90.8%	87.2%	84.0%	93.1%	91.1%	86.1%	100%	>80%

2.3 Grid Generation

Receptor grids were identified using Auto-Dock Tools, Chimera, and Maestro. The grid volume was determined utilising the pocket dimensions, with box size minimised to ensure compatibility with the protein's active site and predicted ligands[19,20]. In addition, it is important to find out if the protein in question is good for medical use. Finding binding sites and evaluating druggability are essential for molecular docking, protein function annotation, cellular activity mechanism clarification, and the development of sensible medications[20-22]. Active sites were identified for binding and grid generation, as shown in Table 2.

2.4 Ligand Preparation

Using MarvinSketch v21.13, ligand molecules were produced and stored in 3D MOL2 format. All compounds were processed and optimised with UCSF Chimaera v1.15 and the AM1-BCC semi-empirical force field, with default steepest descent and conjugate gradient steps of 1000 and 100, respectively[23].

2.5 Molecular Docking

Ligand and protein structures were converted to PDBQT format using the Auto Dock FR (ADFR) suite for protein preparation and AutoDock Tools 1.5.6 for ligand preparation. All ligand rotatable bonds were kept flexible, while receptors were treated as rigid. Docking simulations were carried out using AutoDock Vina version 1.2.3, with a grid spacing of 0.375 Å. The grid box was centred on the active site and set to 20 × 20 × 20 Å^3. Docking parameters included Central Processing Unit (CPU) = 23, exhaustiveness = 32, number of modes = 9, and an energy range of 3[24,25].

Table 2. Grid parameters used for defining the active site during molecular docking of Glycyrrhizic acid with selected viral targets

PDB ID	CENTRE CO-ORDINATES			SIZE CO-ORDINATES		
	X	Y	Z	X	Y	Z
5E84	32.688	-14.185	-39.441	30	30	30
6LU7	-11.514	16.061	67.4	30	30	30
6LZG	-23.866	13.4	-16.44	30	30	30
6M71	227.549	226.92	238.335	30	30	30
6VSB	-48.029	34.785	29.588	30	30	30
6VWW	40.238	-12.061	18.809	40	40	40
6W4B	40.238	-12.061	18.809	30	30	30
6W9C	-37.109	8.793	32.976	40	40	40

2.6 Docking Validation Steps

To verify the reliability of the docking methodology, both redocking and control docking methods were executed. During the redocking phase, the co-crystallised ligand of each target protein, when accessible, was removed and re-docked into its original binding site utilising the identical docking parameters. The accuracy of the docking method was demonstrated by comparing the resultant poses with the experimental conformations and determining that an RMSD (root-mean-square deviation) value of ≤ 2.0 Å was acceptable. To confirm the selectivity of the binding pocket and scoring function for targets lacking co-crystallised ligands, control docking was performed using a known inhibitor or a structurally unrelated decoy molecule. The docking protocol's dependability and reproducibility were validated by consistent binding conformations and anticipated interaction patterns. The docking protocol's dependability and reproducibility were validated by obtaining consistent binding conformations and anticipated interaction patterns across repeated simulations. Docking was performed using AutoDock Vina with ligands treated as flexible, and receptors kept rigid, using a grid box of 20 × 20 × 20 Å^3 centred on the active site, a grid spacing of 0.375 Å, exhaustiveness of 32, nine output modes, an energy range of 3, and CPU = 23[26].

2.7 Visualisation and Analysis

Biovia Discovery Studio Visualiser was used to display the docking results. Complexes were represented in two and three dimensions using LigPlus 1.2 and Maestro 12.3 (academic version). Binding energies and interactions were assessed and contrasted with those of traditional inhibitors. Pharmacodynamic properties were investigated using SWISS-ADME (http://www.swissadme.ch/) for parameters including lipophilicity, water solubility, and drug-likeness rules. The web servers PROTOX (http://tox.charite.de/protox_II/) and pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction) were used for the toxicity analysis to predict tolerance levels in human and animal models, including AMES toxicity, LD50, maximum tolerated dose, and hepatotoxicity[27,28].

2.8 Molecular Dynamics Simulation

Molecular dynamics simulations of 6LZG complexes with ribavirin and Glycyrrhizic acid were performed using Desmond 2020.3 with Optimised Potentials for Liquid Simulations (OPLS)-2005 force field and explicit solvent model with SPC[29-31]. water molecules in a 10×10×10 Å periodic boundary solvation box[32]. The system was neutralised with a 0.15 M NaCl solution. Following system setup, equilibration was performed first under the Number of Particles, Volume, Temperature (NVT) ensemble for 10ns and subsequently under the Number of Particles, Pressure, Temperature (NPT) ensemble for 12ns. Temperature was maintained at 27°C using the Nosé–Hoover chain thermostat (relaxation time 1.0ps), while pressure was kept at 1 bar with the Martyna–Tuckerman–Klein barostat (relaxation time 2ps). Long-range electrostatics were treated with the particle mesh Ewald method using a 9 Å cutoff, and a timestep of 2fs was used with the Reference System Propagator Algorithm (RESPA) integrator. Final production simulations of 100ns were run for 6LZG_Apo, 6LZG_Ribavirin, and 6LZG_Glycyrrhizic acid. Trajectory stability and complex behaviour were assessed through Root Mean Square Deviation (RMSD), Root Mean Square Fluctuation (RMSF), radius of gyration, and hydrogen-bond analysis[33-35].

2.9 Binding Free Energy Analysis

Molecular mechanics generalised Born surface area (MM-GBSA) technique calculated binding free energies using the last fifty frames of simulation trajectories[36]. The binding free energy (ΔG_bind) was calculated using the OPLS_2005 force field and the Variable Surface Generalised Born (VSGB) solvation model by the Python software thermal_mmgbsa.py.:

ΔG_bind is calculated as the sum of ΔG_MM and ΔG_Solv, subtracting ΔG_SA.

Here, ΔG_MM represents the difference between free energies of ligand-protein complexes and isolated components, ΔG_Solv represents the difference in solvation energies, and ΔG_SA represents the difference in surface area energies.

3. Results and Discussion

3.1 Molecular Docking Results

Structure-based molecular docking was employed to identify compounds potentially inhibiting respiratory influenza viruses, including Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1 and 2). Glycyrrhizic acid from liquorice was screened and compared to the commercially available antiviral drug ribavirin using *in silico* methods against nine protein structures.

Primary screening revealed that Glycyrrhizic acid exhibited docking scores ranging from -9.6 to -7 kcal/mol across different targets. Notably, Glycyrrhizic acid showed the highest docking score of -10.307 kcal/mol against the spike receptor-binding domain (6LZG), significantly exceeding the standard ribavirin (-6.18 kcal/mol) against the same target.

Two-dimensional interaction diagrams revealed the binding modes of Glycyrrhizic acid with all nine protein targets. Molecular docking analysis indicated that Glycyrrhizic acid demonstrated the highest binding energy of -10.307 kcal/mol with the spike receptor-binding domain, facilitated by a single hydrogen bond with a lysine residue. Standard ribavirin exhibited -8.855 kcal/mol binding energy against neuraminidase from H1N1. Hydrophobic interactions played crucial roles in ligand-target binding (Table 3).

3.2 Molecular Dynamics Simulation Analysis

3.2.1 Root Mean Square Deviation (RMSD)

The 100ns Molecular Dynamics (MD) simulation trajectories showed that 6LZG_Glycyrrhizic acid exhibited RMSD increase until 75ns, then stabilised with an average RMSD of 2.51 Å. The Apo state stayed constant throughout, with an average RMSD of 2.62 Å. 6LZG_Ribavirin gradually increased over 52 ns until

Table 3. Docking scores (ΔG in kcal/mol) for ribavirin and Glycyrrhizic acid against nine viral protein targets

Molecule	5E84	6LU7	6LZG	6M71	6VSB	6VWW	6W4B	6W9C	5NZ4
Ribavirin	-8.825	-6.61	-6.18	-6.151	-6.067	-6.921	-4.847	-5.867	-8.855
Glycyrrhizic Acid	-7.707	-8.949	-10.307	-9.533	-8.525	-8.125	-7.638	-9.406	-9.358

stabilising with an average RMSD of 2.47 Å. All three states exhibited RMSD values below 3 Å, signifying stable conformations. Compared to the complexes of ribavirin and Glycyrrhizic acid, the Apo state showed somewhat more variations.

3.2.2 Root Mean Square Fluctuation (RMSF)

RMSF analysis revealed variable fluctuations throughout residue indices for all complexes. Sharp peaks appeared around residues 116-120 in all three states, indicating naturally mobile loop regions. 6LZG_Ribavirin showed pronounced peaks at residues 116-121, 137-138, 272, and 408-410. 6LZG_Glycyrrhizic acid exhibited significant fluctuations around residues 83 and 117-120. Critical observation confirmed that fluctuations occurred primarily in loop regions outside the binding site.

3.2.3 Radius of Gyration (Rg)

Rg analysis indicated protein compactness over simulation time. The ranges were: 6LZG_Apo (24.33-28.79 Å), 6LZG_Ribavirin (24.41-33.34 Å), and 6LZG_Glycyrrhizic acid (24.46-28.32 Å). Glycyrrhizic acid complex showed the most compact structure, while ribavirin complex exhibited less compactness. All complexes demonstrated dynamic behaviour with Rg fluctuations, providing insights into conformational changes influenced by compound binding.

3.2.4 Hydrogen Bond Analysis

Hydrogen bond analysis over 100 ns revealed that 6LZG_Ribavirin formed 0-6 hydrogen bonds, suggesting transient or weak bonding. 6LZG_Glycyrrhizic acid exhibited higher and more consistent hydrogen bonding (0-8 bonds), indicating stronger and more stable interaction. The consistency and number of hydrogen bonds suggested potentially higher binding affinity for Glycyrrhizic acid, valuable for understanding therapeutic effects and drug design strategies.

Table 4. Binding free energy components obtained by MM-GBSA analysis for the 6LZG–Ribavirin and 6LZG–Glycyrrhizic acid complexes

Energies (kcal/mol)	6LZG_ Ribavirin	6LZG_ Glycyrrhizic acid
ΔG_{bind}	-56.50±3.28	-69.20±4.18
ΔG_{bind}**Lipo**	-19.46±2.83	-10.15±3.46
ΔG_{bind}**vdW**	2.74±0.83	1.38±0.72
ΔG_{bind}**Coulomb**	-0.94±0.13	-3.30±0.23
$\Delta G_{bind}H_{bond}$	-16.99±0.73	-26.31±1.13
ΔG_{bind}**SolvGB**	22.24±1.59	22.44±2.74
ΔG_{bind}**Covalent**	-42.22±1.85	-51.77±1.47

3.3 MM-GBSA Binding Free Energy Calculations

MM-GBSA analysis from MD simulations revealed comprehensive binding energy profiles for protein-ligand complexes (Table 4).

3.4 Key Findings

- Overall Binding Energy: Glycyrrhizic acid (-69.20 kcal/mol) demonstrated significantly stronger binding affinity than Ribavirin (-56.50 kcal/mol)
- Lipophilic Interactions: Both ligands showed favourable lipophilic interactions, with Ribavirin exhibiting a more significant contribution
- Van der Waals Interactions: Positive values for both ligands suggested weaker or repulsive vdW interactions
- Coulombic Interactions: Glycyrrhizic acid showed stronger electrostatic interactions (-3.30 kcal/mol) compared to Ribavirin (-0.94 kcal/mol)
- Hydrogen Bonding: Glycyrrhizic acid exhibited substantially stronger hydrogen bonding energy (-26.31 kcal/mol) compared to Ribavirin (-16.99 kcal/mol)
- Solvent Effect: Both ligands showed comparable unfavourable solvent contributions upon binding
- Covalent Interactions: Glycyrrhizic acid demonstrated stronger covalent interactions (-51.77 kcal/mol) than ribavirin (-42.22 kcal/mol)

The superior binding affinity of Glycyrrhizic acid can be attributed to its significant lipophilic, Coulombic, hydrogen bonding, and covalent interactions with the 6LZG protein target.

4. Conclusion

Respiratory viral infections represent a significant global health challenge. Natural substances have garnered increasing interest for developing innovative antiviral treatments. This study investigated Glycyrrhizic acid,

a triterpene glycoside from liquorice root (*Glycyrrhiza glabra*), as a potential antiviral agent against respiratory influenza viruses, including SARS-CoV-1 and 2.

Our computational analysis demonstrated that Glycyrrhizic acid:

- Exhibits superior binding affinity compared to the standard antiviral drug Ribavirin across multiple viral protein targets.
- Shows the strongest binding against spike receptor-binding domain (6LZG) with -10.307 kcal/mol docking score.
- Demonstrates stable protein-ligand complexes throughout 100ns molecular dynamics simulations.
- Forms more consistent and numerous hydrogen bonds compared to Ribavirin.
- Achieves lower binding free energy (-69.20 kcal/mol), indicating stronger interaction.
- Complies with Lipinski's rule of five for drug-likeness.
- Shows an acceptable toxicity profile suitable for human consumption.

These findings support the potential development of Glycyrrhizic acid as an inhibitor of critical viral protein targets including spike receptor-binding domain, main protease, RNA-dependent RNA polymerase, spike glycoprotein, ATP-bound state of BiP, and ATP-bound state of BiP, RNA-dependent RNA polymerase, papain-like protease, NSP15 endoribonuclease, neuraminidase from H1N1, and Nsp9 RNA-binding protein.

The data presented here provide valuable insights for determining lead molecules for future *in vitro* and *in vivo* studies (cell-based antiviral assays, enzyme inhibition studies, and binding affinity measurements), supporting therapeutic discovery and development against respiratory influenza viruses, including SARS-CoV-1 and 2. Further experimental validation such as enzyme inhibition, viral entry blocking, or cell-based antiviral studies, to experimentally confirm the predicted activity to confirm these computational predictions and advance Glycyrrhizic acid toward clinical applications.

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Author Contribution

AS: Conceptualisation, experimental work, manuscript drafting, analysis and interpretation. SB: Conceptualisation, data collection, analysis and interpretation, supervision. RY: Manuscript drafting. JS: Analysis and interpretation, manuscript drafting, supervision. UK: Analysis and interpretation, manuscript drafting. All authors have read and agreed to the published version of the manuscript.