WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A Review Article on Biological Activity Studies of Liquorice Using Computer Aided Drug Design

[a] Benitta Joy, [b] Albin Reji

[a] Student, 8th SEMESTER BPHARM, Chemists college of Pharmaceutical Sciences and Research, Ernakulam, Kerala
[b] Student, 8th SEMESTER BPHARM, Chemists college of Pharmaceutical Sciences and Research, Ernakulam, Kerala

A B S T R A C T

Liquorice have a plenty of biological activity which can be predicted using computer aided drug technology. This work is done to computationally evaluate the biological activity of licorice (Glycyrrhiza glabra L.) and elucidate their molecular targets. Methods like permeability prediction, molecular docking, molecular dynamic simulation (MDS) and target predictions are used. By this studies we can conclude that licorice extracts are antioxidants that could boost dermal and epidermal properties. These compounds also have an inhibitory effects on several viruses, including SARS-CoV-2 and thus helps in fighting against COVID-19 and promote immunity boost. The pathways, enrichment studies , and drug-likeness are calculated which shows that the pharmacological activity of liquorice was found to be more than 0.7. Liquiritigenin and Isoliquiritin exhibit ameliorative effects against COVID-19. ADMET screening confirms that the abovementioned components are having better drug-likeness.Insilco pharmacological assessments helps in delivering cost-effective drugs. Liquorice flavonoids (LCFs) also posses anti-melanoma activities in vitro. HipHop method is used to predict the 3D-QSAR pharmacophore model. Furthermore , computational approaches are used to study the effect of licorice against P. vivax. The interaction of licorice compounds with the DARC binding site of DBP was studied using molecular docking. Licochalcone A, echinatin, and licochalcone B were effective against DBP. Thus licorice compounds can be used as a good candidates for novel agents against DBP-mediated RBC invasion of P. vivax. These compounds are used in cosmetic preparations due to their skin-whitening, antisensitizing, and anti-inflammatory properties. These compounds have cosmeceutical effects which is a mixture of both cosmetic and therapeutic like property. The rhizomes and roots are used in the production of functional foods and food supplements.

Keywords: molecular docking , molecular dynamic simulation, hiphop method, pharmacophore , autodock , QSAR

The two main chemical components of liquorice, glycyrrhizin and glycyrrhetinic acid, are classified as triterpenoids. Through the gastrointestinal system, glycyrrhizin is metabolised to create glycyrrhetinic acid, which likewise has numerous pharmacological effects. Perhaps most intriguing is its antiviral action. Hepatitis C virus, herpes simplex type 1, influenza virus, and coronaviruses linked to severe acute respiratory syndrome (SARS) are all inhibited by glycyrrhizin.

1. Antihepatitic Activity

Glycyrrhizic acid has minimal toxicity to host cells and direct anti-hepatitis virus action. In Japan, it has long been used to treat chronic hepatitis. In vitro, glycyrrhizin can prevent HBV surface antigen (HBsAg) from being secreted from PLC/PRF/5 cells. This can result in HBsAg building up in the cytoplasmic vacuoles of the Golgi apparatus, modifications to the intracellular transit of HBsAg, and dose-dependent suppression of its sialylation. At a specific concentration, glycyrrhizin may bind to hepatocytes, alter the expression of HBV-related antigens on hepatocytes, and prevent HBsAg from being sialylated.) When used with lamivudine, glycyrrhizin may prevent HBV replication in a non-Hodgkin lymphoma carrier. Glycyrrhizin has potent anti-HCV properties in addition to its ability to successfully prevent HBV infection.

Glycyrrhizin's antiviral activity in HCV-infected hepatocytes is measured at a safe dose. According to the study findings, at a concentration of 7 ± 1 μg/ml, glycyrrhizin can reduce the titre of the hepatitis C virus (2 x 105 copies of HCV infection) by 50%. Additionally, when combined with interferon, its inhibitory action was amplified. Cyrrhizin is used to treat hepatitis virus infection in addition to interferongly; when taken in conjunction with other medications, this approach has produced better clinical results. Stronger Neo-Minophagen CTM (SNMC), a glycyrrhizin-containing preparation, lowers oxidative stress during HCV treatment in transgenic mice, protecting mitochondria. By blocking PLA2G1B, glycyrrhizin can reduce the release of contagious HCV particles. According to a recent study, glycyrrhetinic acid can significantly reduce the liver inflammatory injury caused by mouse hepatitis virus (1 × 104 PFU/mouse) by blocking the cytokine activity of HMGB1 and inhibiting the release of HMGB1 through the HMGB1-TLR4 signalling pathway. IL-17 and IL-22 levels have been significantly lowered, which is linked to this protective effect instead of a direct prevention of intracellular viral multiplication.

2. Anti-Iinfluenza Virus Activity

Early in the 1980s, reports of glycyrrhizic acid's impact on influenza viruses were made. Through lowering the quantity of haemagglutinin, glycyrrhizic acid was shown in vitro to be able to prevent the influenza virus from replicating in chicken embryos. It has been reported on the mechanism by which glycyrrhizic acid inhibits the reproduction of influenza viruses. The influenza virus can multiply and virus polymerase activity can be increased when HMGB1 and influenza virus nucleoprotein are combined. By opposing this binding effect, glycyrrhizin can lower the activity of influenza virus polymerase and impede the spread of the virus.Glycyrrhizin at therapeutic concentrations prevents the highly pathogenic H5N1 influenza virus from replicating. Additionally, it was discovered that glycyrrhizin prevented H5N1-induced apoptosis and the generation of CXCL10, IL-6, and CCL5 without influencing NK cell function or viral replication.Glycyrrhizic acid and other medications work in concert to create a synergistic effect that guards against influenza virus infection. The study's findings showed that when combined with EW (0.1 μg/kg, 10 μg/kg, and 1,000 μg/kg), glycyrrhizic acid (10 mg/kg body weight) had significant antiviral effects that reduced inflammatory cell infiltration and lung oedema in comparison to EW alone. In mice infected with the H1N1 influenza virus, the use of glycyrrhizic acid in conjunction with the broad-spectrum antiviral medication ribavirin greatly decreased lung consolidation. It was shown that giving 50 mg kg−1 d−1 glycyrrhizin and 40 mg kg−1 d−1 ribavirin together will completely prevent infected mice (5 times the LD50 of influenza H1N1 virus infection), indicating that ribavirin and glycyrrhizin together might have therapeutic benefits.

3.Anti-Human Immunodeficiency Virus Activity

Research has demonstrated that glycyrrhizin suppresses HIV replication in a dose-dependent manner. At 0.6 mM, glycyrrhizin totally blocked both HIV-induced cytopathogenicity and MT-4 cell plaque formation. Furthermore, glycyrrhizin reduces liver dysfunction and boosts the quantity of OKT4 cells, which keeps HIV-positive people with haemophilia from developing AIDS by halting the progression of their disease.Glycyrrhizin has the ability to influence HIV entrance into cells in addition to inhibiting HIV replication. For HIV to enter cells, chemokine receptors or molecules similar to chemokine receptors are required. Glycyrrhizin may stimulate peripheral blood mononuclear cells from HIV-positive patients to produce CCL5 and CC chemokine ligand (CCL) 4. Moreover, glycyrrhizin can lessen the flexibility of the cell membrane, which lessens intercellular fusion and stops HIV from spreading between cells. After adding the replacement media devoid of glycyrrhizin and washing the cells treated with glycyrrhizin, Harada saw a time-dependent increase in the membrane's fluidity as well as an increase in the cells' susceptibility to infection and fusion. This discovery offers a cutting-edge method for treating and preventing enveloped viruses.

4.Anti- Sars-Cov Activity

Scholars initiated an investigation into the protective function of glycyrrhizin against infections caused by the SARS-associated coronavirus (SARS-CoV). After evaluating the antiviral effects of five medications on SARS-CoV, including glycyrrhizin and ribavirin, Cinatl et al. discovered that glycyrrhizin had the greatest inhibitory effect on SARS-CoV replication in Vero cells. Additionally, glycyrrhizin has been shown in studies to suppress the initial phases of the virus replication cycle, namely adsorption and penetration. Moreover, the effects of glycyrrhizin addition on virus adsorption were not as good as those shown subsequent to virus adsorption. Glycyrrhizin's anti-SARS-CoV efficacy can be markedly enhanced by altering its structure, especially by generating amide derivatives and amino acid conjugates, albeit doing so increases cytotoxicity. Clinical symptoms like dyspnea improved quickly in clinical studies, and the glycyrrhizin therapy group did not experience any side effects. The average time for lung lesion improvement from the most severe to 50% decreased.The World Health Organisation (WHO) has designated the coronavirus disease-2019 (COVID-2019) pandemic as a result of the novel coronavirus known as SARS-CoV-2. The gene sequences of SARS-CoV-2 and SARS-CoV exhibit 79.5% homology, and there are several similarities between the clinical signs and symptoms of these two viruses' illnesses. Glycyrrhizin has a number of pharmacological effects, including binding to the enzyme angiotensin-converting enzyme II (ACE2), downregulating proinflammatory cytokines, inducing endogenous interferon, inhibiting intracellular thrombin and R accumulation, and producing excessive amounts of exudates from the airways. These results imply that glycyrrhizin might be a promising medication for the treatment of COVID-19. In a recent study, glycyrrhizin showed no appreciable cytotoxicity and strongly suppressed SARS CoV-2 multiplication in Vero E6 cells in a dose-dependent manner. Yu et al. discovered that glycyrrhizin is the most potent and safe broad-spectrum anti-coronavirus compound in vitro, especially against SARS-CoV-2, using computer-aided drug design and biological verification.

5.Effects On Some Animal Viruses

It has been shown that glycyrrhizin has antiviral action against a few animal viruses. Li et al. used RT-PCR, the plaque reduction test, and CPE observation to examine the impact of glycyrrhizin diammonium on infectious bronchitis virus (IBV) cell infection. The findings showed that glycyrrhizin diammonium can totally prevent cell infection and has direct antiviral effect. Glycyrrhizin has shown good immune-stimulating and antiviral effects against duck hepatitis virus (DHV), either by itself or in combination with the vaccine. IBDV infection can be successfully inhibited by dipotassium glycyrrhizinate, which can both directly inactivate and interfere with IBDV reproduction. When the virus was treated prior to incubation, diammonium glycyrrhizinate (DG) was found to have a potent inhibitory effect on PPV. DG had an antiviral effect on PPV-infected swine testicular (ST) cells. Additionally, DG proved to be antiviral against. Glycyrrhizin mostly prevents PRRSV from penetrating and only little affects PRRSV's adsorption or release over the course of its life cycle. Tong et al. used the hydrothermal technique to synthesise Gly-CDs utilising glycyrrhizic acid and carbon dots (CDs) with great biocompatibility. These Gly CDs have the potential to suppress PRRSV invasion and replication, boost antiviral innate immunity, and prevent intracellular

ROS buildup brought on by PRRSV infection. Although it has no effect on the virus's assembly and release, glycyrrhizin can also prevent the porcine epidemic diarrhoea virus (PEDV) from entering the body and replicating.

6.Cosmetics

6.1. Preparation Of The Ligand

The primary phytochemicals found in Glycyrrhiza glabra (licorice) have been identified, and SMILES format has been obtained for their structures.

6.2.In Silico Pharmacokinetics

For in silico screening of absorption, distribution, metabolism, and excretion (ADME), the SMILESs of each ligand were employed. Based on a model by Potts and Guy, the in silico pharmacokinetics predicted the skin permeation log kp.

According to the following equation:

$\log kp\ (cm/s) = 0.71 * \log kow - 0.0061 * MW - 6.3$

MW = the molecular weight of the compound

log kow (or log Po/w) = octanol-water partition coefficient

High skin penetration compounds were identified for more examination. Using the ligands' SMILESs, hierarchical clustering analysis was also carried out on a ChemMine web server.

6.3.Prediction Of Insilico Target

Using a SwissTargetPrediction server, the chosen ligands with high skin-permeability coefficients based on anticipated pharmacokinetics were employed for target prediction.

6.4.Molecular Docking Studies

Ten common molecular target proteins with anti-inflammatory, anti-oxidant, and dermatocosmetic properties had their three-dimensional structures determined. Using the ACDLab/Chemsketch programme, the structures of ligands with high skin penetration were optimised in three dimensions and stored in mol format. The ligand file was converted from mol to pdb using PyMol software, and protein chain A was prepared by removing water and preexisting ligands. Using AutoDock Tools, ligands and proteins were ready for docking, and the resulting file was saved in pdbqt format.

6.5.Molecular Docking Program

The docking experiment was conducted using AutoDock Vina. Using ezLigPlot on an ezCADD web server, close interactions of the target's binding with the ligands were examined and visualised following docking.

6.6.Protein–Protein Interaction Analysis

The gene IDs of ten common molecular target proteins for anti-inflammatory, antioxidant, and dermatocosmetic actions were examined in order to determine the link between the expected targets of licorice phytochemicals and high skin permeability.

6.7.Protein–Ligand Molecular Dynamics Simulation

Using Desmond, Schrödinger LLC, molecular dynamics simulations were run for 100 nanoseconds. The docking investigations provided the starting points for the protein and ligand complexes used in the molecular dynamics simulation. Using Maestro's protein preparation wizard, which also includes complex optimisation and minimization, protein–ligand complexes were preprocessed. The System Builder tool was used to prepare all systems. To determine the Transferable In termolecular Interaction Potential 3 Points (TIP3P), a solvent model with an orthorhombic box was chosen. The simulation made use of the Optimised Potential for Liquid Simulations (OPLS)-2005 force field. In order to replicate physiological conditions, 0.15 M NaCl counterions were added to the models to make them neutral. For a full simulation, the NPT ensemble at 300 K in temperature and 1 atm in pressure was chosen.

In order to replicate physiological conditions, 0.15 M NaCl counterions were added to the models to make them neutral. For a full simulation, the NPT ensemble at 300 K in temperature and 1 atm in pressure was chosen. Before the simulation began, the models were loosened. Throughout the simulation, the trajectories were saved every 100 ps. The root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), radius of gyration (Rg), solvent accessibility surface area (SASA), and protein–ligand interaction profile were found through post-simulation analysis of the trajectories.

Prime molecular mechanics/generalized Born surface area (MMGBSA) was calculated as follows: MMGBSA $\Delta G^{bind} = \Delta G^{complex} - \Delta G^{protein} - \Delta G^{ligand}$

MMGBSA ΔG^{bind} (NS) = $\Delta G^{complex} - \Delta G^{protein*} - \Delta G^{ligand*}$

MMGBSA ΔG^{bind} (NS) = MMGBSA $\Delta G^{bind} - \Delta G^{protein\_strain} - \Delta G^{ligand\_strain}$

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