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In silico docking study of selected compounds for its hepatoprotective activity

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Abstract

Liver fibrosis is a condition characterized by the excessive accumulation of scar tissue in the liver. It is typically caused by chronic liver diseases, such as chronic viral hepatitis (e.g., hepatitis B and C), alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis, and certain genetic conditions. Ephrin receptor A2 (EphA2) is identified as potential anti-inflammatory target which influences inflammatory process and immune response, impacting the recruitment and activation of immune cells and as a host cofactor for Hepatitis C Virus (HCV) entry. Andrographolide a diterpenoid lactone, Scoulerine a natural alkaloid possess anti-inflammatory activity. The present work was done to evaluate anti-inflammatory activity of andrographolide and scoulerine using software Autodock 4.2. Phyto-constituents were fetched from the PubChem database. 3D structure of EphA2 were downloaded from Protein Data Bank (PDB). Among two phyto compounds, andrographolide had highest binding energy of -7.58 which is a clear evident of potential anti-inflammatory activity and prevent hepatic fibrosis. The active site of the target protein was predicted by using CASTP (Computed atlas of surface topography of proteins). Protein ligand interaction information is obtained by Protein ligand interaction profiler.

Keywords: Andrographolide; Scoulerine; Protein Data Bank; Anti-inflammatory; Autodock 4.2

1 Introduction

The Aim of present study is to evaluate phyto compounds andrographolide and scoulerine for their anti-inflammatory activity and prevent hepatic fibrosis. Since hepar is the Greek word for liver, terms associated with liver in medicine frequently begin with hepato or hepatic. [1] Liver plays a crucial function in metabolism, secretion and storage and is frequently known as the “great chemical factory” of the body. The liver plays a critical role in the body's control, synthesis, storage, and secretion of various important proteins, minerals, and chemicals, as well as in the removal of toxins and excess substances. The liver secretes bile, which is among other things essential to digestion. The danger of liver toxicity has increased due to recent increases in exposure to pesticides, pharmaceuticals, environmental contaminants, and routine chemotherapy use. Liver injury is invariably associated with cellular necrosis, an increase in tissue lipid peroxidation, and a decrease in tissue glutathione (GSH) levels. Additionally, there is an increase in the serum levels of various biochemical indicators, including triglycerides, cholesterol, bilirubin, alkaline phosphatase, serum glutamate oxaloacetate transaminase (SGOT/AST) and serum glutamate pyruvate transaminase (SGPT/ALT) [2]. EphA2 act as co-receptors for hepatitis C Virus (HCV) entry and influences inflammatory process and immune response, impacting the recruitment and activation of immune cell, inhibition of EphA2 is emerging as a new approach to counteract HCV infection. As one of the functional targets for miR-200a in hepatocellular carcinoma, EphA2 was found to be overexpressed during inflammation. Eph receptors are thought to be the largest family of receptor tyrosine kinases (RTKs), and they are involved in numerous biological processes like cell adhesion, cell migration, and angiogenesis. EphA2 also showed enhanced expression in the liver in the Lipopolysaccharide injection model of sepsis. Fibronectin

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deposition requires the expression of EphA2. Depletion of EphA2 diminishes extracellular matrix deposition. Thus, the molecular target chosen to stop inflammation-induced liver damage is the EphA2 receptor tyrosine kinase. [3]

1.1 Hepatotoxicity

Hepatotoxin is a toxic chemical substance which damages the liver. Hepatotoxicity is the term used to describe the toxic or harmful effects of substances on the liver. It refers to the ability of certain drugs, chemicals, toxins, or other agents to cause damage to the liver, disrupting its normal structure and function. This damage can result in a range of liver-related health issues, from mild liver enzyme elevations to severe liver diseases, including hepatitis, fibrosis, cirrhosis, and even liver failure. Hepatotoxicity can manifest in various ways and may lead to symptoms such as jaundice, abdominal pain, fatigue, and changes in liver enzyme levels in blood tests. It is a significant concern in the fields of medicine and toxicology, as identifying and managing hepatotoxicity is crucial for patient health and safety caused by herbal supplements, diosyncratic responses, diet, medication, alcohol, toxins, chemicals, viruses, autoimmune diseases, metabolic disorders, and diet [4].

1.2 Phytochemicals profile

1.2.1 Andrographolide

Andrographolide is a diterpenoid lactone found in the plant Andrographis paniculata, also known as the "King of Bitters."

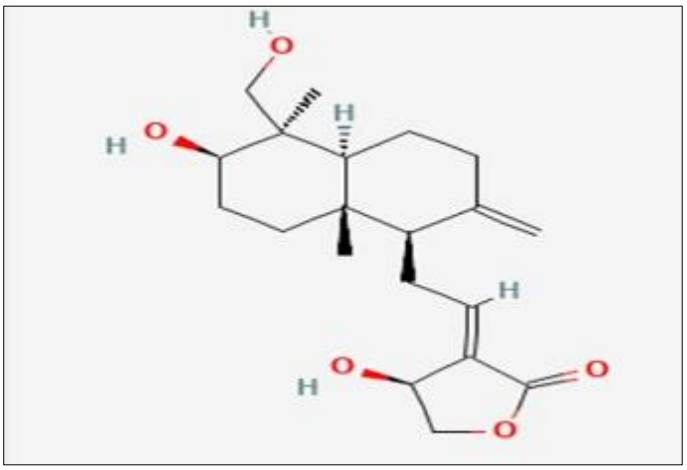


Figure 1 Structure of Andrographolide

1.2.2 Mechanism of Action

- Antioxidant activity: Andrographolide has been found to possess antioxidant properties, which can help neutralize harmful free radicals and reduce oxidative stress in the liver cells.
- Anti-inflammatory effects: The compound has shown anti-inflammatory properties, which could help reduce inflammation in the liver and prevent further damage.
- Modulation of liver enzymes: Andrographolide may influence certain liver enzymes involved in detoxification processes, promoting the elimination of harmful substances and protecting liver cells.
- Immune modulation: It is suggested that Andrographolide can modulate the immune response, potentially reducing immune-mediated damage to the liver. These mechanisms collectively contribute to andrographolide's hepatoprotective effects, making it a object of interest in the field of liver health research [5].

Table 1 General Information about Andrographolide

1.	**Molecular Formula**	$C_{20}H_{30}O_5$
2.	**IUPAC**	(3E,4S)-3-[2-[(1R,4aS,5R,6R,8aS)-6-hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-2-methylidene-3,4,4a,6,7,8-hexahydro-1H-naphthalen-1-yl]ethylidene]-4-hydroxyoxolan- 2-one
3.	**Source**	Leaves and stem of *Andrographolide paniculata* plant
4.	**Medicinal properties**	Anti-inflammatory Antioxidant Immunomodulatory Anti-viral Anti-bacterial
5.	**Health support**	Respiratory health Digestive health Immune support Hepatoprotective
6.	**Chemical safety**	Irritant
7.	**Molecular Weight**	350.4 g/mol

1.3 Scoulerine

Scoulerine is a natural product benzylisoquinoline alkaloid found in Sarcocapnos saetabensis, Corydalis bungeana, and other organisms. It is also found in various plant species, particularly in some members of the Papaveraceae family. Plants such as Chelidonium majus (celandine) and Corydalis yanhusuo (yanhusuo, or Chinese corydalis). [6].

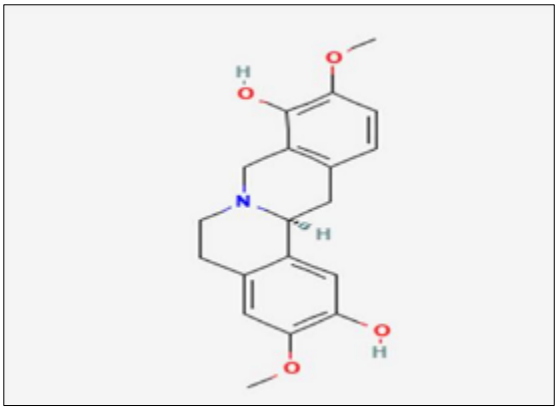


Figure 2 Structure of scoulerine

Table 2 General information about scoulerine

1. Molecular Formula	$C_{19}H_{21}NO_4$
2. IUPAC	3,10-dimethoxy-6,8,13,13a-tetrahydro-5H-isoquinolino[2,1-b]isoquinoline-2,9-diol
3.Source	alkaloid found in Sarcocapnos saetabensis, Corydalis bungeana, and other organisms
4.Medicinal properties	Anti-inflamatory Antioxidant Hepatoprotective Anaglesic Anti-microbial Cardiovascular effect
5.Molecular Weight	327.4 g/mol

2 Materials and methods

2.1 Protein Preparation – EphA2 Receptor

The protein used in this study was obtained from the Protein Data Bank. The URL is https://www.rcsb.org/structure/1MQB. 1MQB is the PDBID. The protein is created using Autodock software 4.2, wherein the raw structure is integrated with the inclusion of hydrogen atoms, bond order assignment, charge fixing, and group orientation [8]. Docking experiments are conducted using the target protein's optimized PDB coordinates, which have a stable conformation and minimal energy. The anti-inflammatory target for liver fibrosis was determined to be ephA2. Amino acid residues such as Glu 623, Lys 646, Glu 663, Thr 692, Tyr 694, Met 695, Glu 696, Ala 699, Tyr 735, Arg 743, Asp 744, and Ser 756 are present in the green pocket, which has a surface volume of 2297.72 and a mass of 1330.96.

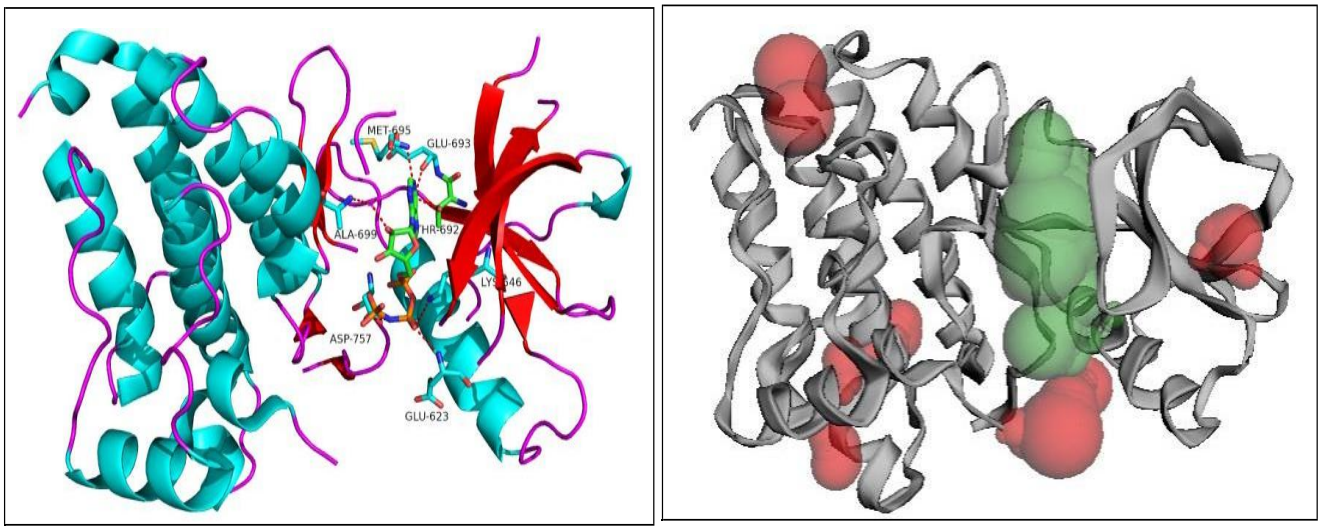


Figure 3 3D Structure of EPHA2 Protein with binding sites depicted as green and redpockets

2.1.1 Active Site Prediction

Using the target protein's PDB file as the server's input, the target protein's active site was predicted using the CASTP (Computed Atlas of Surface Topography of Proteins) server. The pockets were identified as the protein's active site residues. http://castp/index.html?1mqb; sts.bioe.uic.edu. The pocket where tiny molecules (ligands) have the most surface area to transfer energy to the target (protein) [9].

2.2 Ligand preparation

2.2.1 Phytochemicals

Three phytochemicals were screened against EphA2. The list of compounds is shown in Table.

Table 3 List of ligands with IUPAC Name

Silymarin	3, 5, 7-trihydroxy-2-[3-(4-hydroxy-3-methoxyphenyl)-2- (hydroxymethyl)-2,3-dihydro-1, 4-benzodioxin-6-yl]-3,4- Dihydro-2H-1-benzopyran-4-one is a flavonolignan.
Andrographolide	(3E,4S)-3-[2-[(1R,4aS,5R,6R,8aS)-6-hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-2-methylidene-3,4,4a,6,7,8- hexahydro-1H-naphthalen-1-yl]ethylidene]-4- hydroxyoxolan-2-one
Scoulerine	3,10-dimethoxy-6,8,13,13a-tetrahydro-5H-isoquinolino[2,1-b]isoquinoline-2,9-diol

These compounds, along with standard drug silymarin have been fetched from Pubchem. These chemicals are prepared using Autodock 4.2. To undertake docking investigations, Auto dock removes water, adds hydrogen, adds charges, and removes heteroatoms [10]. It then creates low energy structures with the right chiralities and ionization states and stabilizes them structurally.

Table 4 Center grid box

1.	X-center	48.4
2.	Y-center	33.137
3.	Z-center	48.453

2.3 Pharmacokinetic Studies of Phytochemicals

Preadmet is a web-based application which provides numerical information related to absorption, distribution, metabolism, excretion, and toxicity (ADMET) data and building drug-like library using in-silico method. Bioactive compound will be of no use if their pharmacokinetic properties are not appropriate. Pre ADMET tool (http://preadmet.bmdrc.kr) helps to save time and money before the synthesis of compounds by filtering the best compounds during the early stage of drug discovery.

2.4 Molecular Docking

Using IFD, all three compounds' molecular docking against the EphA2 receptor was completed. Silymarin is used as the reference inhibitor against EphA2. The lowest binding energy determines which compound is the best. The findings show that andrographolide and scoulerine have a strong affinity for the EphA2 protein in terms of docking score, glide energy, and interactions with the residues in the active site (ILE779A). Given that it complied with the Lipinski rule of five and had strong hepatoprotective effects, it is regarded as the best chemical [11].

3 Results

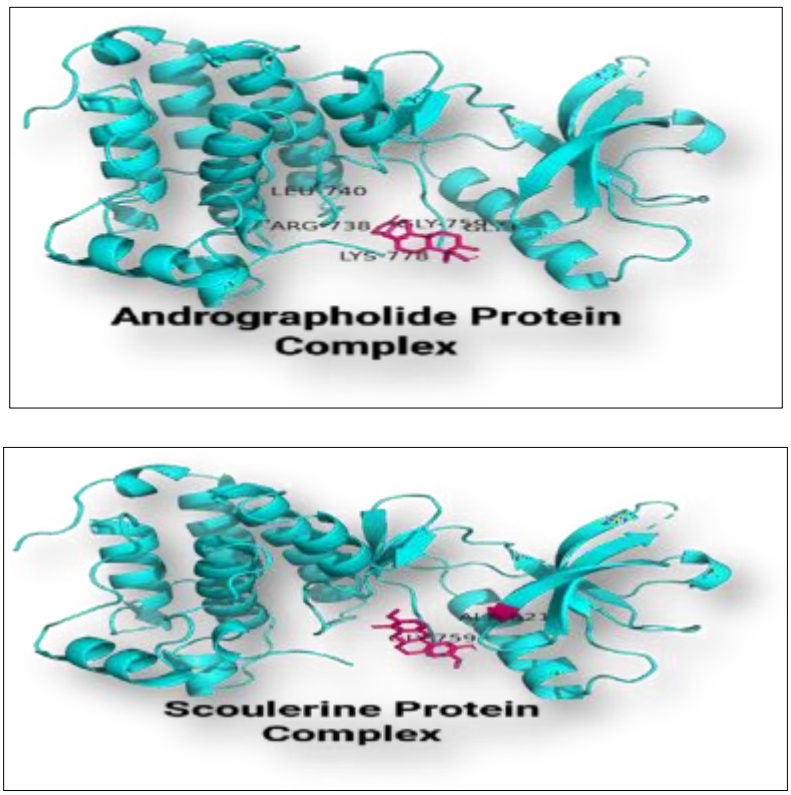
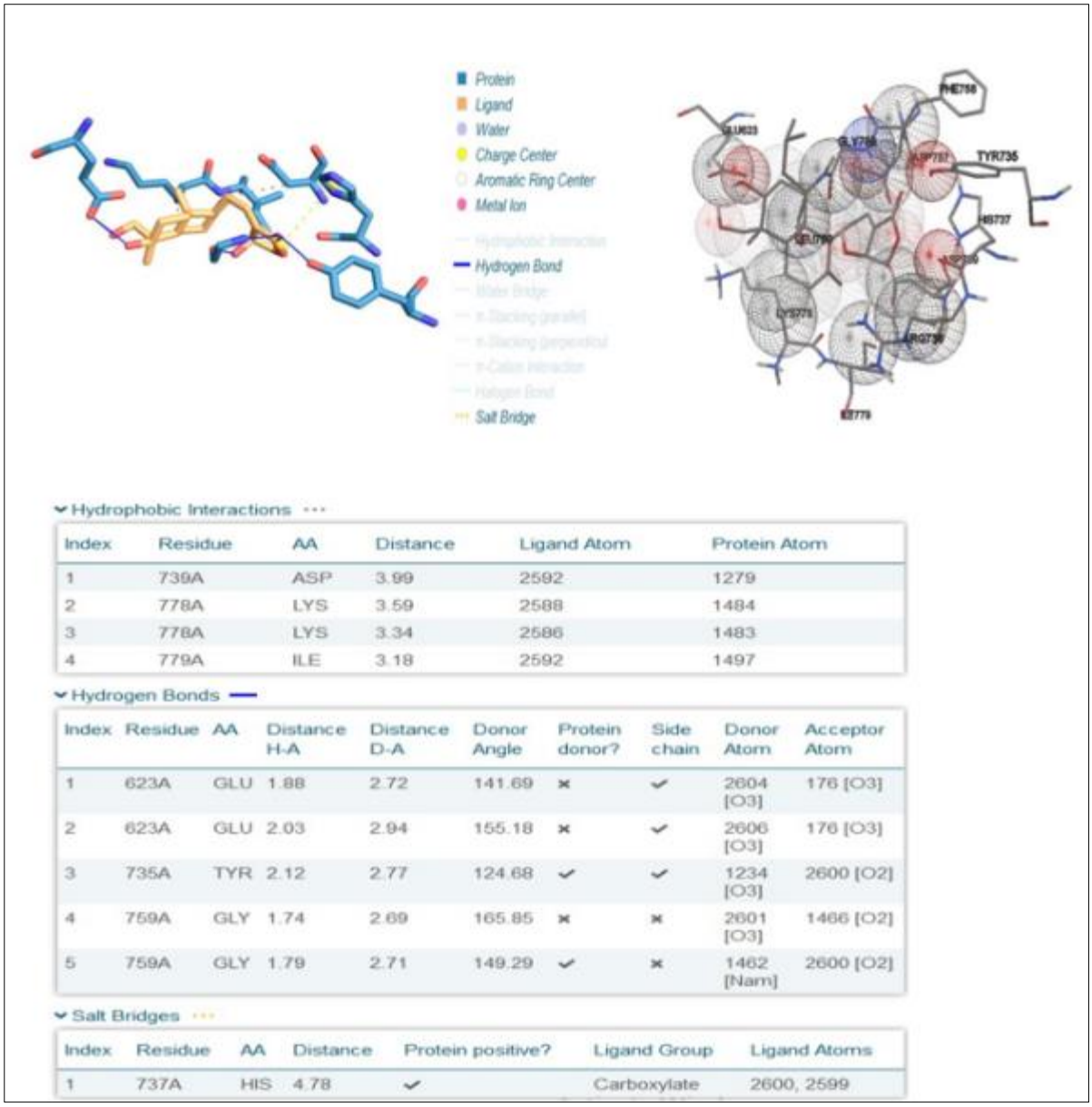


Figure 4 Protein Complex of Andrographolide and Scoulerine

3.1 Protein ligand interaction profile

The data has been obtained using protein ligand interaction profiler



Hydrophobic Interactions

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	739A	ASP	3.99	2592	1279
2	778A	LYS	3.59	2588	1484
3	778A	LYS	3.34	2586	1483
4	779A	ILE	3.18	2592	1497

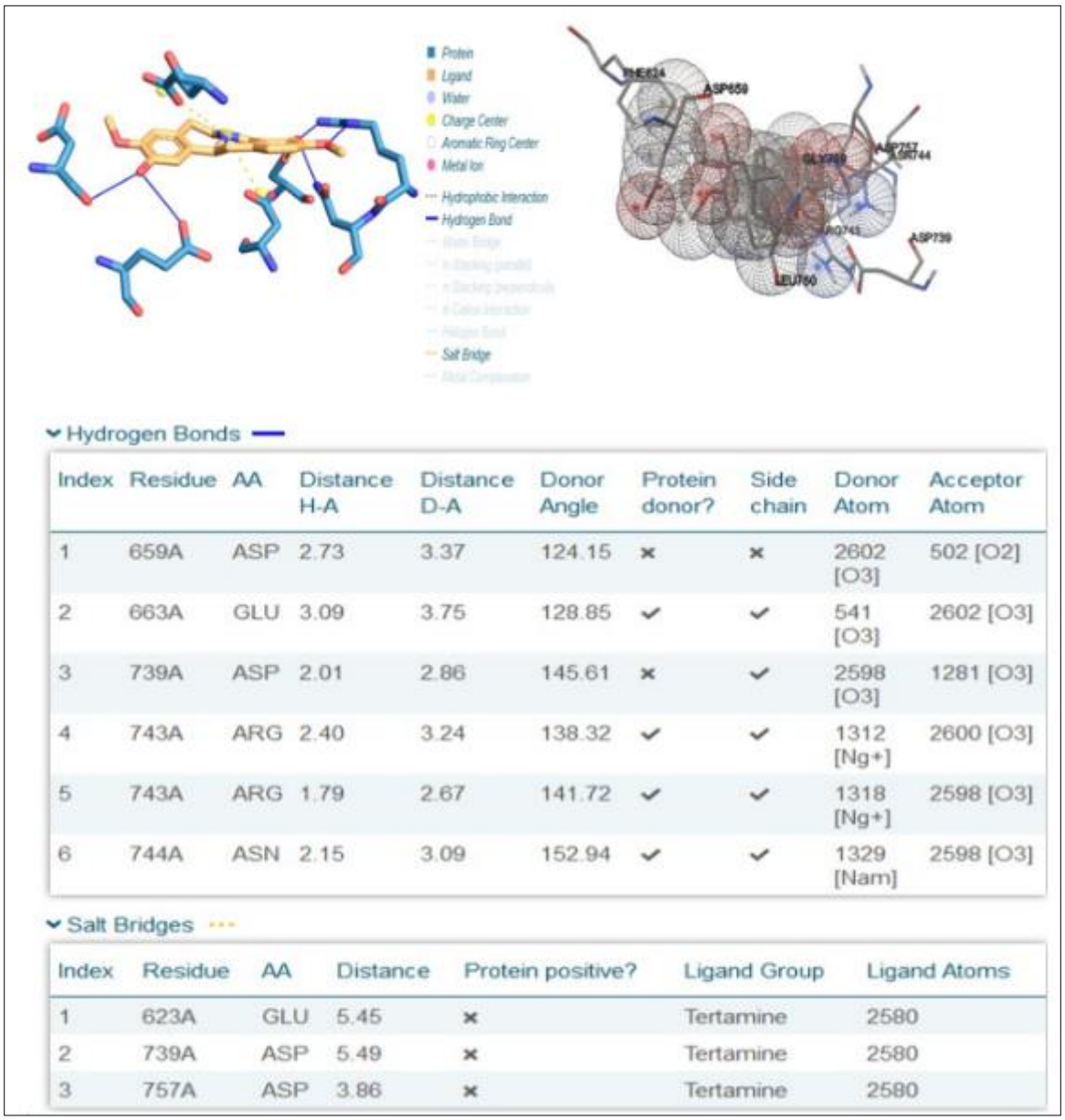
Hydrogen Bonds

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Side chain	Donor Atom	Acceptor Atom
1	623A	GLU	1.88	2.72	141.69	✗	✓	2604 [O3]	176 [O3]
2	623A	GLU	2.03	2.94	155.18	✗	✓	2606 [O3]	176 [O3]
3	735A	TYR	2.12	2.77	124.68	✓	✓	1234 [O3]	2600 [O2]
4	759A	GLY	1.74	2.69	165.85	✗	✗	2601 [O3]	1466 [O2]
5	759A	GLY	1.79	2.71	149.29	✓	✗	1462 [Nam]	2600 [O2]

Salt Bridges

Index	Residue	AA	Distance	Protein positive?	Ligand Group	Ligand Atoms
1	737A	HIS	4.78	✓	Carboxylate	2600, 2599

Figure 5 Andrographolide Protein interaction profile



Hydrogen Bonds

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Side chain	Donor Atom	Acceptor Atom
1	659A	ASP	2.73	3.37	124.15	×	×	2602 [O3]	502 [O2]
2	663A	GLU	3.09	3.75	128.85	✓	✓	541 [O3]	2602 [O3]
3	739A	ASP	2.01	2.86	145.61	×	✓	2598 [O3]	1281 [O3]
4	743A	ARG	2.40	3.24	138.32	✓	✓	1312 [Ng+]	2600 [O3]
5	743A	ARG	1.79	2.67	141.72	✓	✓	1318 [Ng+]	2598 [O3]
6	744A	ASN	2.15	3.09	152.94	✓	✓	1329 [Nam]	2598 [O3]

Salt Bridges

Index	Residue	AA	Distance	Protein positive?	Ligand Group	Ligand Atoms
1	623A	GLU	5.45	×	Tertamine	2580
2	739A	ASP	5.49	×	Tertamine	2580
3	757A	ASP	3.86	×	Tertamine	2580

Figure 6 Scoulerine Protein interaction profile

Table 5 Docking Scores

Compound	Phytoconstituent	Binding energy
Standard	SILYMARIN	-8.29
Test	ANDROGRAPHOLIDE	-7.58
Test	SCOULERINE	-7.10

4 Discussion

Using IFD, the three molecular docking against the EphA2 receptor was completed. In that they produce connections akin to those of ATP, tyrosine kinase inhibitors function similarly to ATP. Silymarin serves as the reference inhibitor for EphA2 [12]. The lowest binding energy produced by the hydrogen bond interaction is used to determine which molecule

is the best. The phytochemical IFD results are listed in the table above. According to the data, compound 1 andrographolide binds to the EphA2 protein with a high affinity (measured by binding energy and docking score) and interacts with the residues located in the active site (739A ASP, 778A LYS, and 779A ILE). and form hydrogen bonds with 759A GLY, 735A TYR, and 623A GLU. Because it followed the Lipinski rule of five, it is thought to be the best compound. , and also it possesses high hepatoprotective activity. The interaction above illustrates the hydrogen bond that andrographolide forms with the EphA2 receptor. Compound 2: Scoulerine demonstrates a strong binding energy and demonstrated good hepatoprotective effect in its interactions with the EphA2 proteins ASP 649A, GLU 663A, ASP 739A, ARG 743A, and ASN 744A [13, 14]. Compound 2 had a strong affinity for the EphA2 protein and formed hydrogen bonds with GLU 623A, ASP 739A, and ASP 739A, as the following diagram illustrates. The common medication silymarin exhibited a strong affinity for EphA2 and formed hydrogen bonds with Gly 625, Met 695, Arg 743, Asp 757, and Lys 646 [15, 16]. Two key components of the receptor were visible in the pharmacophore of the EphA2 active site. EphA2's ATP binding site, Lys 646, is known to be the target location for a large number of inhibitors. Residues close to Lys 646 can likewise be utilized to prevent the receptor from becoming phosphorylated by ATP.

5 Conclusion

The results from this study helped to find Andrographolide as one of the bioactive compound having highest binding affinity towards EphA2 receptor responsible for the hepatoprotective effect by exhibiting anti-inflammatory activity. The information gathered from this study can be applied to the design of hepatoprotective medications that target new targets in liver fibrosis through experimental research.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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