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MOLECULAR DOCKING STUDIES ON PHYTOCHEMICALS OF *SOLANUM NIGRUM* FRUITS FOR ITS HEPATOPROTECTIVE ACTIVITY

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Keywords:

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ABSTRACT: Liver fibrosis is a wound healing process that is initiated in response to chronic liver injury caused by viruses, toxins, and hepatotoxic drugs. This disease is characterized by inflammation, followed by the deposition of extracellular matrix proteins to form scar tissue. Ephrin receptor A2 (EphA2) is identified as a host cofactor for Hepatitis C Virus (HCV) entry. The fruits of *Solanum nigrum* possess anti-inflammatory properties. The present work was done to evaluate the anti-inflammatory activity of the ethanolic fruit extract of *Solanum nigrum* against EphA2 receptor using Induced fit docking of Schrödinger software. Phyto-compounds were retrieved from the PubChem database. The 3D structure of EphA2 was downloaded from Protein Data Bank (PDB). Among the five phytocompounds, Ethyl caffeate has the Glide Score of -8.01 and glide energy-35.48 kcal/mol. From the results, it is evident that the phytoconstituents of *Solanum nigrum* fruits have anti-inflammatory potential and prevent hepatic fibrosis. Molecular properties of the compounds were predicted using the Molinspiration tool, and the pharmaco-kinetic properties of the compounds were predicted using the Preadmet tool. Anti-inflammatory and hepatoprotective activities of the compounds were assessed using PASS online tool. The knowledge gained from this work can be further used in experimental studies to design hepatoprotective drugs against novel targets involved in liver fibrosis.

INTRODUCTION: The liver performs the central role in detoxification and transformation of toxic chemicals, so it is exposed to their deleterious effect, which increases its susceptibility to various diseases. Globally over 10% of the population is suffering from liver diseases. Some of the common liver diseases are hepatitis, fibrosis, cirrhosis, hepatic steatosis (fatty liver), alcoholic liver disease and drug-induced liver problems [1]. Wound repair is a vital process in the liver in which the extracellular matrix (ECM) composition and stiffness are essential.

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During chronic liver injury, continuous ECM remodeling takes place, leading to uncontrolled deposition of extracellular proteins, carbohydrates, and proteoglycans. This process leads to fibrosis, which is one of the causes of mortality associated with liver failure [2]. Chronic liver injury is caused by hepatitis viral infection, excessive alcohol consumption, hepatotoxic drugs, and metabolic disorders. Chronic inflammation is an immune response in which tissue remodeling and wound healing processes take place simultaneously [3].

EphA2 act as co-receptors for hepatitis C Virus (HCV) entry and inhibition of EphA2 is emerging as a new approach to counteract HCV infection [4]. EphA2 was identified as one of the functional targets for miR-200a in hepatocellular carcinoma [5]. EphA2 show enhanced expression in the liver in the Lipopolysaccharide injection model of sepsis [6].

Eph receptors are regarded as the largest family of receptor tyrosine kinases (RTKs), and it is involved in many biological processes such as cell adhesion, cell migration, and angiogenesis. EphA2 is overexpressed during inflammation [7]. EphA2 expression is required for fibronectin deposition [8]. EphA2 depletion reduces extracellular matrix deposition [9].

So, the EphA2 receptor tyrosine kinase is selected as the molecular target to prevent liver disease initiated by inflammation. The synthetic drugs available to treat liver diseases damage the liver. Hence, there is a preference for herbal drugs because of its efficacy, safety, and low cost [10]. Medicinal plants serve as an important ingredient in the development of drug molecules [11]. *Solanum nigrum* is commonly used as a traditional medicine to treat various diseases. It is widely used in India and in other parts of the world for the treatment of liver disorders and peptic ulcer [12].

It is used as an antioxidant, anti-tumorigenic, hepatoprotective, anti-inflammatory agent in the oriental system of medicine [13]. Computational docking is extensively used during the drug discovery and development process. It is used to predict the bound conformation and binding free energy of small molecules (ligands) to the target (protein) [14]. ADMET (absorption, distribution, metabolism, excretion, and toxicity) studies are used in an earlier stage of the drug discovery process to avoid the end-stage failure in the finding of new molecules as medicines [15].

MATERIALS AND METHODS:

Protein Preparation – EphA2 Receptor: Protein for the present work was retrieved from Protein Data Bank (http://www.rcsb.org) [PDBID: 1MQB]. The 3-dimenstional structure of EphA2 protein in complex with phosphoaminophosphonic acid-denylate ester (ANP) was represented using Pymol in **Fig. 1**.

ANP is an analog of ATP. Receptor protein is prepared using Protein Preparation Wizard of Schrödinger software 2015 [16] where the addition of hydrogen atoms, assigning bond orders, fixing of the charges, and orientation of groups were incorporated into the raw structure.

The optimized PDB coordinates of target protein had minimum energy and possess stable conformation, which is taken further to perform docking studies. EphA2 was chosen as an anti-inflammatory target for liver fibrosis.

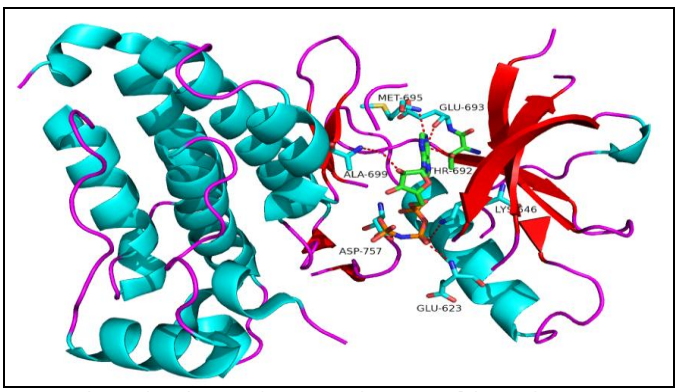


FIG. 1: 3D STRUCTURE OF EPHA2 PROTEIN (CHAIN A) WITH ANP DEPICTED AS GREEN COLOUR

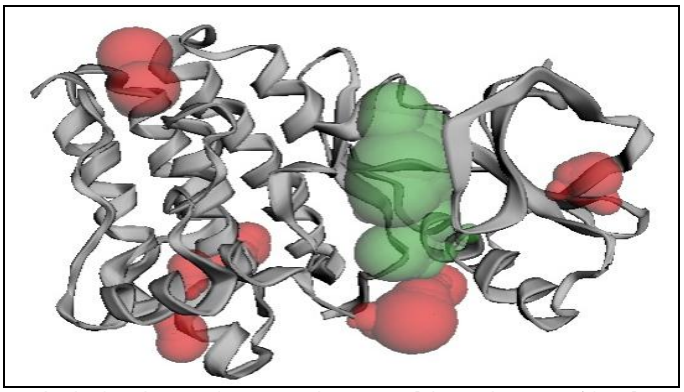


FIG. 2: 3D STRUCTURE OF EPHA2 PROTEIN (CHAIN A) WITH BINDING SITES DEPICTED AS POCKETS (GREEN – POCKET 1; RED – POCKET 2, 3, 4 AND 5)

Active Site Prediction: The active site of the target protein was predicted by using CASTP (Computed atlas of surface topography of proteins) server PDB file of the target protein was given as the input in the server.

Active site residues of the protein were defined as the pockets (http://sts.bioe.uic.edu/castp/ index. html). The pocket with maximum surface area of 1330.96 and surface volume of 2297.72 depicted as green pocket contains amino acid residues such as Glu 623, Lys 646, Glu 663, Thr 692, Glu 693, Tyr 694, Met 695, Glu 696, Ala 699, Tyr 735, Arg 743, Asp 744 and Ser 756, pocket 2, 3 and 4 were depicted as red color in **Fig. 2**.

Receptor Based Pharmacophore: Pharmacophore is defined as the essential features present in the

drug-like molecules which are necessary for appropriate binding with the protein.

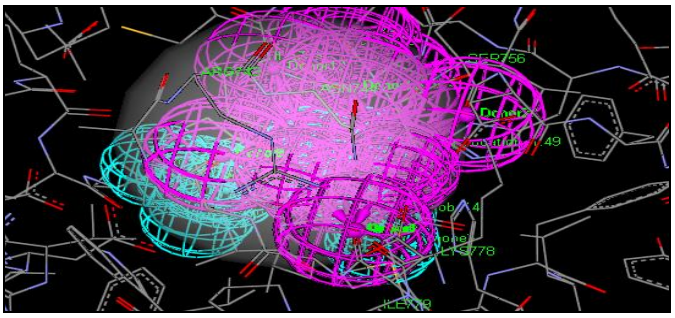
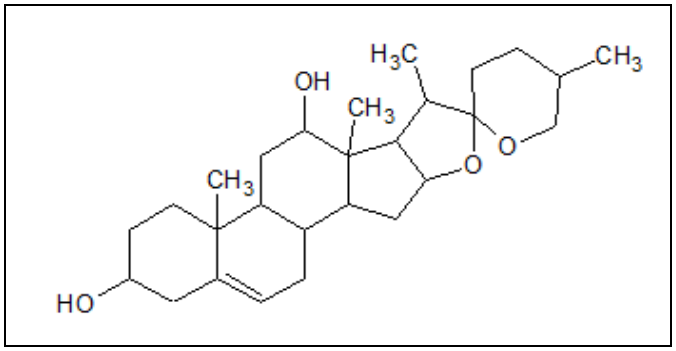


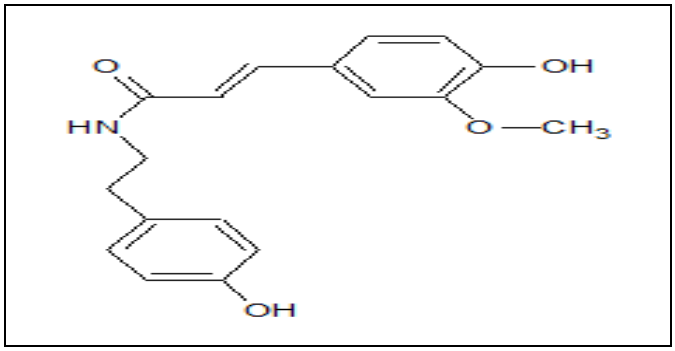
FIG. 3: PHARMACOPHORE MAP OF EPHA2

The reverse approach is applied to find the binding site of the target protein using a receptor-oriented pharmacophore. Receptor based pharmacophore prediction model was generated using EphA2 as the input protein in Biovia Discovery studio [17] with Lys 646 as the active site.

The pharmacophore map of EphA2 showed two essential chemical features: Aliphatic Hydrophobic (Lys 778) are shown as cyan color circles, Hydrogen bond donor (Arg 743, Asp 744, Ser 756) shown as pink color circles in **Fig. 3**.



COMPOUND 1



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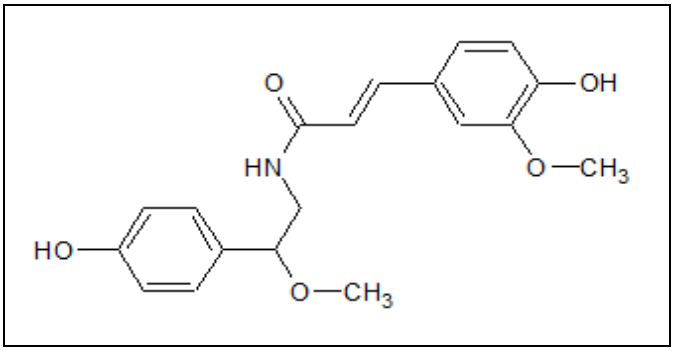
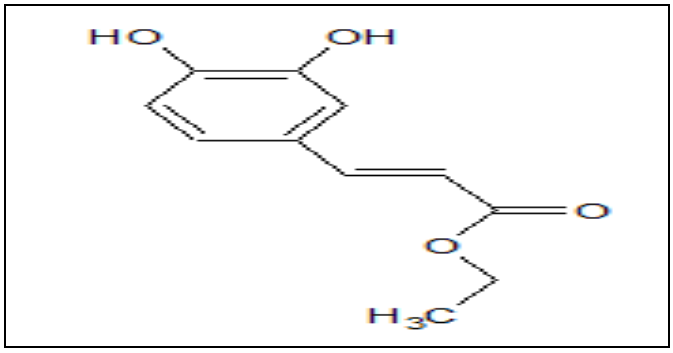
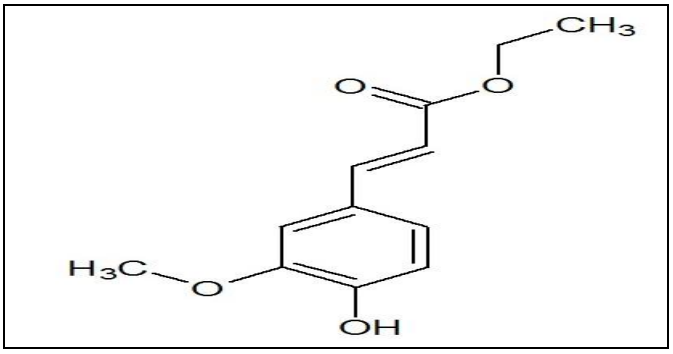


COMPOUND 3



COMPOUND 4



COMPOUND 5

FIG. 4: LINE DIAGRAM OF PHYTOCHEMICALS

Preparation of Ligands – Phytochemicals: Five phytochemicals identified from ethanolic fruit extract of *Solanum nigrum* were screened against EphA2. The list of compounds is shown in **Table 1**. These compounds, along with standard drug silymarin have been retrieved from Pubchem. The line diagram of the compounds is given in **Fig. 4**. These compounds were prepared using Ligprep

module [18] of Schrödinger. Ligprep performs the addition of hydrogens, generates low energy structure with correct chiralities and ionization states. These compounds were energy minimized using steepest descent and conjugate gradient methods of Impact application. This two-step procedure was done to bring the energy level of the compounds to the minimum and make them structurally stable to perform docking studies.

Physicochemical Prediction of Compounds: Determination of the physicochemical property of lead molecules is essential in the drug discovery process. Log P (log octanol/water partition coefficient) value is an important predictor used to find the oral bioavailability of drug molecules. So, we calculated Log P along with other molecular properties such as molecular weight, several hydrogen bond acceptors (O and N), and a number of hydrogen bond donors (NH and OH) of the 5 lead compounds using Molinspiration tool (http://www. molinspiration.com/).

It uses the concept of Lipinski rule of five (molecular weight <= 500 daltons, number of hydrogen bond acceptors <= 10, and number of hydrogen bond donors <= 5, logP <= 5). Molecules violating more than one of these rules may have problems with bioavailability.

TABLE 1: PHYTOCONSTITUENTS FROM *SOLANUM NIGRUM* FRUITS

S. no.	Name of the compound
1	Spirost-5-ene-3β,12 β-diol
2	N-trans-feruloyl-tyramine
3	(R)-3-(4-hydroxy-3-methoxyphenyl)-N-[2-(4-hydroxyphenyl)-2-mehtoxyethylacrylamide
4	Ethyl caffeate
5	Ethyl 4-hydroxy-3-methoxy cinnamate

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 compounds will be of no use if their pharmacokinetic properties are not appropriate. Pre ADMET tool (http://preadmet.bmdrc.kr) helps to filter the best compounds during the early step of drug discovery to save time and cost before the synthesis of compounds.

Prediction of Activity Spectra for Substances (PASS): PASS is an online tool (http://www. pharmaexpert.ru/passonline) used for the evaluation of the biological potential of organic drug-like compounds. This tool can be used to predict various biological activities in a single run based on the structure of the organic compound. PASS tool can be used in the initial process of drug discovery prior to chemical synthesis or extraction of compounds as it estimates the biological activity profile of the virtual compound. Pa is defined as probability "to be active." It denotes the chance that the test compound belongs to the sub-class of active compounds, which resembles the structures of molecules, falling in the sub-set of “actives” in the training set of PASS. Pi is defined as the probability "to be inactive." It calculates the chance that the test compound belongs to the sub-class of inactive compounds, which resembles the structures of molecules falling in the sub-set of "inactive" in the PASS training set.

Induced Fit Docking (IFD): Molecular docking of a small molecule with the receptor is a well known computational method used to predict the interactions between two molecules. The active site geometry of a protein complex depends heavily upon conformational changes induced by the bound ligand. IFD module [19] of Schrödinger, predicts the ligand-induced conformational changes in receptor active sites. All computational works were performed on red hat enterprise linux workstation using the molecular modeling software Schrodinger using OPLS-AA (Optimized Potential liquid simulation for All Atom) force field.

The docking of compounds to the ATP binding site (Lys 646 of the kinase domain) of EphA2 was performed using IFD. IFD generates multiple poses of the ligand complex, each including unique structural modifications of the receptor to fit the ligand pose and ranks these poses by docking score and glide energy [20]. The best confirmation with the lowest docked energy is selected. The interactions of complex enzyme-ligand conformations, including hydrogen bond, were analyzed using Pymol [21] and it was used to generate quality images of the docked complex.

RESULTS AND DISCUSSION: The physico-chemical properties of the compounds from Molin-

spiration are given in **Table 2**. These results were used for the screening of the compounds based on their molecular properties. Lipinski screening analysis revealed that all the selected compounds except compound 1 (Milogp – 5.02) possessed drug-likeness property and they are taken further for the docking process.

TABLE 2: PHYSICOCHEMICAL PROFILE FOR *SOLANUM NIGRUM* COMPOUNDS

S. no.	Compound (Pubchem Id)	Milogp [a]	TPSA[b]	MW[c]	n.ON[d]	n.OHNH[e]	n.rotb[f]
1	99568060	5.02	58.92	430.63	4	2	0
2	5280537	2.43	78.79	313.35	5	3	6
3	643362	2.20	88.02	343.38	6	3	7
4	5317238	1.93	66.76	208.21	4	2	4
5	736681	2.24	55.77	222.24	4	1	5

[a]MilogP - Molinspiration logP, [b]TPSA – Total polar surface area, [c]MW - Molecular weight, [d]n. ON - number of hydrogen bond acceptors O and N, [e]n. OHNH - number of hydrogen bond donors OH and NH, fn. rotb - number of rotatable bonds

Computational Evaluation of Biological Activity: In order to narrow down the research for potent natural products, the prediction of activity spectra for substances (PASS) prediction program was used to predict the anti-inflammatory and hepatoprotective activities. From the results given in **Table 3**, it is inferred that compound 4 was found to possess high anti-inflammatory (Pa-0.636) as well as hepatoprotection (Pa-0.559) activities. Compound 1 showed high anti-inflammatory Pa value, but this compound violate Lipinski rule of five in the molecular property prediction.

TABLE 3: PASS PREDICTION FOR *SOLANUM NIGRUM* COMPOUNDS

S. no.	Compound	Anti-inflammatory		Hepatoprotectant	
		Pa	Pi	Pa	Pi
1	Compound 1	0.733	0.012	0.385	0.384
2	Compound 2	0.297	0.163	0.406	0.031
3	Compound 3	0.406	0.021	0.361	0.040
4	Compound 4	0.636	0.025	0.559	0.016
5	Compound 5	0.602	0.031	0.597	0.012

Pa- probability "to be active"; Pi-probability "to be inactive."

TABLE 4: PHARMACOKINETIC PREDICTION RESULTS OF *SOLANUM NIGRUM* COMPOUNDS

ADMET	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5
Absorption					
HIA	93.77	90.00	90.12	89.45	94.67
Caco-2	42.42	21.65	21.56	21.28	29.49
MDCK	0.27	72.36	1.85	181.26	270.23
SP	-3.37	-3.43	-3.45	-2.14	-1.88
Distribution					
BBB	3.07	1.24	0.52	0.19	0.07
PPB	90.80	82.03	79.82	61.02	62.82
Metabolism					
CYP450 3A4 inhibition	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Non-inhibitor
CYP450 2C9 inhibition	Inhibitor	Non-Inhibitor	Inhibitor	Inhibitor	Inhibitor
CYP450 2C19 inhibition	Non-Inhibitor	Non-Inhibitor	Non-Inhibitor	Inhibitor	Inhibitor
CYP450 2D6 inhibition	Non-Inhibitor	Non-Inhibitor	Non-Inhibitor	Non-Inhibitor	Non-Inhibitor
Excretion					
P-gp Inhibition	Inhibitor	Non- inhibitor	Non- inhibitor	Non- inhibitor	Non- inhibitor
Toxicity					
hERG_inhibition	Low risk	Medium risk	Medium risk	Medium risk	Medium risk
Carcino_rat	Negative	Negative	Negative	Negative	Negative

Human intestinal absorption (HIA), Caco human epithelial colorectal adenocarcinoma cell line, Madin Darby Canine Kidney cell line (MDCK), Skin permeability (SP), Plasma protein binding (PPB), Blood-brain barrier (BBB), P-glycoprotein transporter (P-gp), human ether-a-go-go-related gene (hERG) and Rodent carcinogenicity (Carcino rat)

ADMET Prediction: Prediction of pharmaco-kinetic properties is helpful in the drug develop-ment process to increase the success rate of a lead compound to emerge as a drug and it will help to minimize the cost. From the Preadmet results given in **Table 4,** all compounds were found to possess a good ADMET profile and can be taken for docking studies.

Molecular Docking: The molecular docking of all five compounds from *Solanum nigrum* fruit was carried out against the EphA2 receptor using IFD. Tyrosine kinase inhibitors mimic ATP, in the sense that they make interactions similar to what ATP makes. Silymarin is used as the reference inhibitor against EphA2. The best compound is selected based on the lowest Glide (binding) energy generated by hydrogen bond interaction. IFD results for the phytochemicals are tabulated in **Table 5**. The results indicate that compound 4, Ethyl caffeate has a high binding affinity with EphA2 protein in terms of Glide energy, docking score, and it made interaction with the active site residues (Lys 646) of the kinase domain. It is taken as the best compound as it obeyed Lipinski rule of five, and also it possesses high hepatoprotective activity in PASS prediction. The hydrogen bond interaction formed by Ethyl caffeate with the EphA2 receptor is shown in **Fig. 5A**. Compound 5, Ethyl ferulate has good binding energy, and it made interaction with the Lys 646, Asp 757, and Met 695 of EphA2 is shown in **Fig. 5B** and it showed good hepatoprotective activity. Compound 2 had a high binding affinity with EphA2 protein and it made hydrogen bond interaction with Asp 757, Glu 663 shown in **Fig. 5C**. Standard drug Silymarin showed a high binding affinity with EphA2, and it made hydrogen bond interaction with Gly 625, Met 695, Arg 743, Asp 757 and Lys 646 shown in **Fig. 5D**. In this study, the knowledge of hot spots (binding sites) for ligand binding is used for focusing on structure-based pharmacophore prediction.

TABLE 5: DOCKING RESULTS OF *SOLANUM NIGRUM* COMPOUNDS WITH EPHA2 RECEPTOR

Compound	Docking score	Glide energy (kcal/mol)	Binding residues	H-Bond Interaction (Å)
1	-6.99	-46.86	Lys 646 (NH...O)	2.7
			(OH...O) ASP 757	1.9
			MET 695 (NH...O)	2.0
			(OH...O) GLU 693	2.1
2	-8.12	-48.17	Lys 646 (NH...O)	2.4
			(OH...O) Glu 663	2.6
			(OH...O) Glu 663	1.8
			(NH...O) Asp 757	1.9
			Met 695 (NH...O)	2.1
			(OH...O) GLU 693	2.2
3	-8.49	-37.21	Lys 646 (NH...O)	2.7
			Ser 756 (OH...O)	2.3
			(OH...O) Met 695	2.1
			Met 695 (NH...O)	1.9
			Ala 621 (NH...O)	2.9
4	-8.01	-35.48	Lys 646 (NH...O)	2.1
			(OH...O) Met 695	2.5
			(OH...O) Met 695	1.8
			Met 695 (NH...O)	1.8
5	-5.77	-34.95	Lys 646 (NH...O)	2.2
			(OH...O) ASP 757	1.8
			Met 695 (NH...O)	1.9
Silymarin (standard drug)	-9.69	-51.30	(OH...O) Gly 625	2.2
			Arg 743 (NH...O)	2.3
			Met 695 (NH...O)	2.3
			(OH...O) Asp 757	1.9
			(OH...O) Met 695	1.7

The pharmacophore of the active site of EphA2 showed two essential features present in the receptor. It is known that Lys 646 is the ATP binding site of EphA2, which is the target site for many of the inhibitors. Other than Lys 646, residues nearby to it can also be used to inhibit the ATP-phosphorylation of the receptor. The essential features are one Lipo (Aliphatic hydrophobic) Lys 778 and three hydrogen bond donor features (Arg 743, Asp 744, Ser 756). These residues were found around 10Å of the ATP binding site Lys 646. Hence this structure-based approach can be used further to screen a list of inhibitors and can be filtered based on their interactions with the essential features of EphA2.

The salt bridge formed between Lys 646 and Glu 663 is conserved, which coordinates α and β phosphate groups of ATP. Lys 646 is the important residue required for salt bridge formation. The interaction mediated by Met 695 seemed to be important, since this residue forms a part of the gatekeeper residue.

Met 695 sterically control the binding of compound 4 to hydrophobic regions adjacent to the ATP-binding site Lys 646. Compound 5 formed hydrogen bond with Asp 757, Lys 646, and Met 695 of EphA2 receptor. Asp 757 was found to be the key residue since it forms a part of Asp-Phe-Gly (DFG) motif. This motif lies within the EphA2 protein kinase domain and adjacent to the ATP-binding site. The DFG aspartate is believed to be important for catalysis, and indeed typically points into the ATP binding site (the DFG-in conformation).

The active site residues found to be interacting with the bioactive compounds were more significant because they were more closely located around the binding site. So, if any alterations are made to these residues, it will affect the phosphorylation of ATP in the receptor. Hence, these phytochemical compounds can be used to inhibit EphA2 kinase to ameliorate liver injury induced by persistent inflammation.

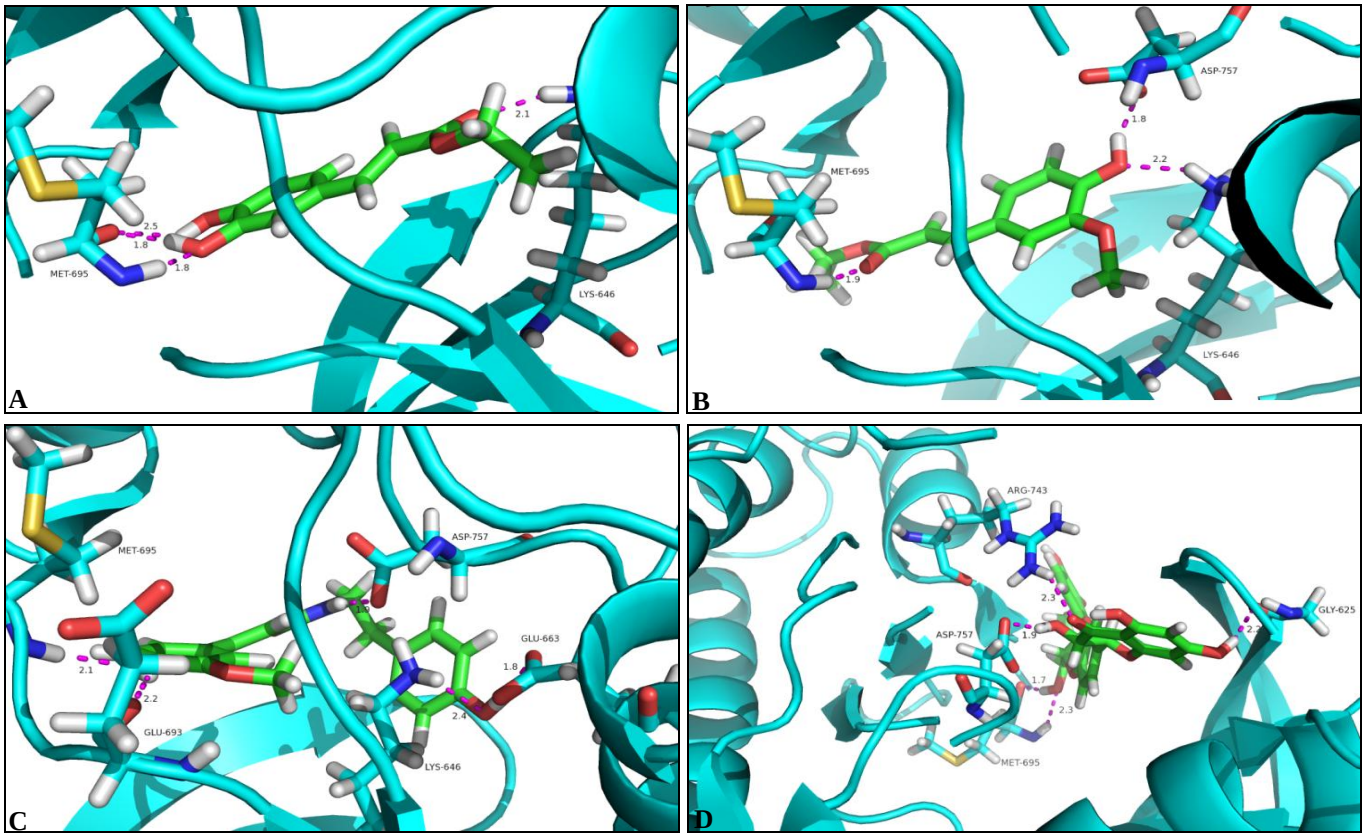


FIG. 5: FAVOURABLE BINDING CONFORMATION OF BIOACTIVE COMPOUNDS WITH EPHA2 (PDB ID: 1MQB) MEDIATED BY HYDROGEN BOND INTERACTION (PINK COLOUR DOTTED LINES). A) THE THREE DIMENSIONAL DIAGRAM SHOWS THE INTERACTION OF COMPOUND 4 WITH AMINO ACID RESIDUES LYS 646 AND MET 695 B) BINDING OF COMPOUND 5 WITH EPHA2 ACTIVE SITE. C) INTERACTION OF COMPOUND 2 WITH EPHA2 ACTIVE SITE. D) INTERACTION OF STANDARD HEPATOPROTECTIVE DRUG SILYMARIN AT THE ATP-BINDING SITE OF EPHA2

CONCLUSION: The present results indicate that the receptor-based pharmacophore prediction of the EphA2 receptor is effective for determining the essential amino acid residues involved in drug-target interaction. Molecular property calculation, ADMET and PASS-prediction results of the selected natural compounds were helpful in finding the efficient bioactive lead with the required properties. It would save unnecessary wastage of chemicals and time during the drug development process. The results from this study helped to find Ethyl caffeate as one of the bioactive compounds responsible for the hepatoprotective effect of *Solanum nigrum* fruit. It showed hepatoprotection

by exhibiting anti-inflammatory activity against the EphA2 receptor. Further experimental studies are being carried out to validate our results.

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CONFLICTS OF INTEREST: All authors declare that there are no conflicts of interest in the present study.

CONTRIBUTION OF THE AUTHORS: The first author, U. Mythily, did design experimental part of the work and writing of the manuscript. The plan of work was done by Dr. S. Subramaniam. Correction of the Manuscript was done by Dr. S. Subramaniam.

REFERENCES:

1. Latief U and Ahmad R: Herbal remedies for liver fibrosis: A review on the mode of action of fifty herbs. Journal of Traditional and Comple Medicine 2018; 8(3):352-360.
2. Baiocchini A, Montaldo C, Conigliaro A, Grimaldi A, Correani V and Mura F: Extracellular matrix molecular remodelling in Human liver fibrosis evolution. PLOS One 2016; 11(3): e0151736.
3. Tanaka M and Miyajima A: Liver regeneration and fibrosis after inflammation. Inflammation and Regeneration 2016; 36(19): 1-6.
4. Wang J, Zheng X, Peng Q, Zhang X and Qin Z: Eph receptors: the bridge linking host and virus. Cellular and Molecular Life Sciences 2019. DOI: 10.1007/s00018-019-03409-6.
5. Xu Y, Zhang Y, Wang L, Zhao R, Qiao Y and Han D: miR-200a targets Gelsolin: A novel mechanism regulating secretion of microvesicles in hepatocellular carcinoma cells. Oncology Reports 2017; 37(5): 2711-19.
6. Funk SD, Finney AC, Yurdagul AJr, Pattillo CB and Orr AW: EphA2 stimulates VCAM-1 expression through calcium dependent NFAT1 activity. Cellular Signalling 2018; 49: 30-38.
7. Finney AC, Funk SD, Green JM, Yurdagul A Jr, Rana MA and Pistorius R: EphA2 expression regulates inflammation and fibro proliferative remodelling in atherosclerosis. Circulation 2017; 136(5): 1-26.
8. Finney AC and Orr AW: Guidance molecules in vascular smooth muscle. Frontiers in Physiology 2018; 9: 1311.
9. Li RX, Chen ZH and Chen ZK: The role of EPH receptors in cancer-related epithelial-mesenchymal transition. Chinese Journal of Cancer 2014; 33(5): 231-40.
10. Rane J, Jadhao R and Bakal RL: Liver diseases and herbal drugs: a review. J of Inno in Pharm and Biol Sci 2016; 3(2): 24-36.
11. Shakya AK: Medicinal plants: Future source of new drugs. International Journal of herbal medicine 2016; 4(4): 59-64.
12. Krithika R and Verma RJ: *Solanum nigrum* confers protection against CCl_4-induced experimental hepato-toxicity by increasing hepatic protein synthesis and regulation of energy metabolism. Clinical Phytoscience 2019; 5(1).
13. Mukhopadhyay G, Sarkar S, Kundu S, Kundu S, Sarkar P and Sarkar S: Ethno-pharmacological activity of *Solanum nigrum*. The Pharma Inno Journal 2018; 7(10): 692-98.
14. Forli S, Huey R, Pique ME, Sanner M, Goodsell DS and Olson AJ: Computational protein-ligand docking and virtual drug screening with the Autodock suite. Nature Protocols 2016; 11(5): 905-19.
15. Zhou W, Wang Y, Lu A and Zhang G: Systems Pharmacology in Small Molecular Drug Discovery. Int Journal of Molecular Sciences 2016; 17(2): 246.
16. Maestro, version 10.2, Schrödinger, LLC, New York, 2015.
17. Biovia Dassault Systèmes: Discovery Studio Modeling Environment, Release 4.5, San Diego, USA, 2015.
18. Ligprep, version 3.4, Schrodinger, LLC, New York, 2015.
19. Induced Fit Docking protocol 2015-2, Glide version 6.4, Prime version 3.7, Schrodinger, LLC, New York, 2015
20. Glide, Version 6.7, Schrödinger, LLC, New York, New York, 2015
21. Delano WL: The PyMOL molecular graphics system, version 1.8, Schrödinger, LLC, New York, 2015.

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