

Natural phytochemicals: Potential anti-HCV targets *in silico* approach

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ABSTRACT

Objective: To identify phytochemicals as NS5B inhibitors against viral NS5B polymerase *in silico* model. The NS5B polymerase is a hepatitis C virus (HCV) protein involved in the HCV replication. HCV infection can cause progressive liver damage.

Material and Methods: Molecular docking method is used to identify binding efficiency between the NS5B (PDB ID: 3UPI) and the ligands (phytochemicals), i.e., Gallic acid, Catechin, Resveratrol, Apigenin, and Silibinin. Molinspiration tool is also used to determine the druglikeness properties of ligands (Lipinski's rules of five). The docking results were compared to the reference ligand, Dasabuvir.

Results: The molecular docking study revealed that all phytochemicals were formed complex with the HCV NS5B polymerase via hydrogen bonding interactions. The phytochemicals showed good binding efficacy with the docking score: gallic acid (-5.47 kcal/mol), catechin (-7.31 kcal/mol), resveratrol (-8.14 kcal/mol), apigenin (-8.75 kcal/mol), and silibinin (-10.75 kcal/mol) compared to the reference drug, Dasabuvir (-11.43 kcal/mol).

Conclusion: The docking results suggested that all phytochemicals showed good binding affinity against hepatitis NS5B polymerase which might be due their antiviral properties.

INTRODUCTION

Hepatitis C virus (HCV) is the major causative agent of Hepatitis C disease. Its infection leads to chronic liver diseases, such as hepatitis, cirrhosis, and hepatocellular carcinoma or liver failure. It is the most common endemic liver diseases worldwide affecting approximately 71 million people (WHO, 2017). In viral hepatitis, hepatocytes cells are replaced by tough and non-functional fibrous tissue (Clin, 2009). The HCV is a micro RNA virus belonging to a member of the Flaviviridae family. Its genetic material is the ribonucleic acid (RNA) which encodes the structural proteins (Core proteins E1 and E2) and the nonstructural proteins include NS3 protease and NS5B RNA dependent RNA polymerase (Thayailany *et al.*, 2015). NS5B protein has been considered as a target to design and develop noble anti-HCV

agents. The nonstructural protein 5B (NS5B), an RNA dependent RNA polymerase, is responsible for the replication of HCV genome (Varun *et al.*, 2014). It has been clinically tested that NS5B plays a central role in the HCV replication. Most of the current drugs target this enzyme for the treatment of hepatitis C diseases. Hence, NS5B enzyme is considered as a target to design and develop a potential drug against HCV. However, the present antihepatitis drug treatment is expensive, less effective, and has numerous side effects. Thus, specific antiviral agents need to be developed against HCV life cycle.

Medicinal plants have been considered as an alternative source of medicines for the treatment of various human diseases, including liver diseases (Kumar and Pandey, 2013). Experimental studies showed that medicinal plants possess secondary metabolites known as phytochemicals. Many phytochemicals are being tested against hepatitis virus to find the promising antiviral agents. They have been reported to have many medicinal activities, such as anti-oxidant, anti-inflammatory, anti-thrombogenic, anti-mutagenic, anti-allergic, anti-bacterial, anti-cancer, antiviral, neuroprotective, and hepatoprotective (Panche *et al.*, 2016; Shakya, 2016).

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Therefore, the aim of the present study is to investigate medicinal plants derived phytochemicals as NS5B inhibitors against hepatitis C NS5B polymerase *in silico* approach.

MATERIALS AND METHODS

Ligand preparation

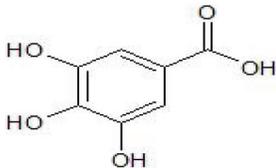
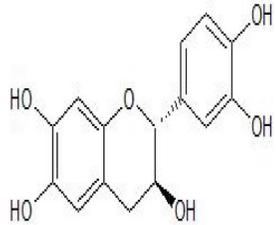
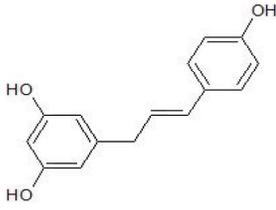
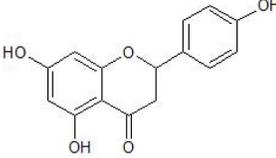
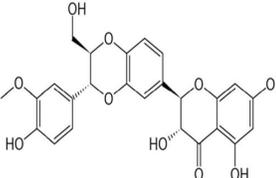
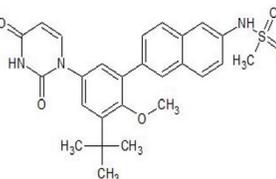
Ligands selected for the protein (NS5B) interactions were based on review of the literature on potential hepatoprotective phytochemicals derived from medicinal plants. Medicinal plants derived phytochemicals along with the reference ligand, Dasabuvir are summarized in Table 1. The chemical structure of ligands was accessed from the PubChem database and drawn in Advanced

Chemistry Development's ChemsKetch which were converted into 3D structure (Programme Database file-PDB) by using the Open Babel software and employed for docking analysis. The Dasabuvir, a known antihepatitis drug, was used as a reference ligand to compare the docking results of phytochemicals (Trivella *et al.*, 2015).

Druglikeness calculation

Molinspiration (<http://www.molinspiration.com/>) is an online tool used to determine the drug-likeness properties of ligands. Lipinski's Rule of Five is a rule of thumb to evaluate druglikeness properties. It states that most "drug-like" molecules

Table 1. Chemical structures of ligands constructed using ChemSketch Software.

Ligands	Rich sources	Chemical structure	Medicinal property
Gallic acid	Gallnuts, Toona sinensis and <i>Terminalia bellerica</i> .		Antioxidant, hepatoprotective (Jadon <i>et al.</i> , 2007) anti-inflammatory, antibiotic, anticancer (Sankar <i>et al.</i> , 2012) and antiviral (Govela-Salas <i>et al.</i> , 2016).
Catechin	<i>Camellia sinensis</i> (a tree plant), Grapes, blueberries, and apple.		Antioxidant, antitumor (Shimamura <i>et al.</i> , 2007) and antihepatitis properties (Rekshmyd'dharan <i>et al.</i> , 2013).
Resveratrol	<i>Vitis vinifera</i> and red wine		Anti-carcinogenic, hepatoprotective (Burns <i>et al.</i> , 2002, Yusub <i>et al.</i> , 2015) and antiviral (Xiao <i>et al.</i> , 2018).
Apigenin	Grapefruit, artichoke, basil, celery and plant-derived beverages		Anti-inflammatory, hepatoprotective, antioxidant, and anti-carcinogenic (Shohreh <i>et al.</i> , 2008; Shukla and Gupta, 2010).
Silibinin	Silymarin marimum		Excellent medicine for liver problems. Hepatoprotective, anticancer and antiviral properties (Fried <i>et al.</i> , 2012; Haddad <i>et al.</i> , 2011), Antiviral (Polyak <i>et al.</i> , 2013).
Dasabuvir	Chemically synthesized		Standard drug for the treatment of Hepatitis C disease.

should have $\log P \leq 5$, molecular weight ≤ 500 , number of hydrogen bond acceptors ≤ 10 , and number of hydrogen bond donors ≤ 5 .

Preparation of protein structure

The crystallographic structure of the NS5B polymerase bound 4, 5-dihydrofurano indole was retrieved from the protein data bank (PDB ID: 3UPI) and the resolution was 2.00 Å (Fig. 1) (Velazquez *et al.*, 2011). The 3UPI protein contains two types of polypeptide chains: A and B. The bound inhibitor 4, 5-dihydrofurano indole (HETATM and CONNECT) was removed from the 3UPI. The protein structure was then optimized using Swiss-PDB viewer software. The optimized structure has minimum energy confirmation which was used for the docking study.

Active site prediction

The NS5B active site was predicted by the online server of Meta Pocket 2.0 (Huang, 2009). The potential amino acid residues at NS5B active site was given in Table 2.

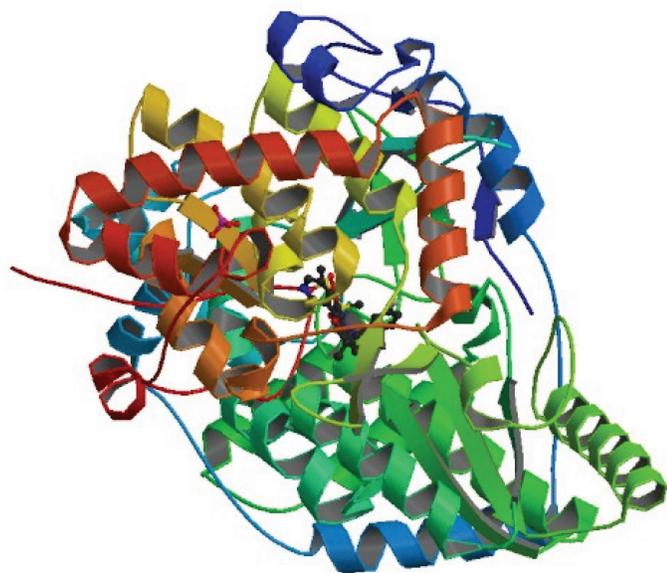


Figure 1. HCV NS5B Polymerase (PDB ID: 3UPI).

Docking studies

The docking of all the phytochemicals toward the active site of the 3UPI (NS5B) targets was conducted using the AutoDock 4.2 tool (Morris *et al.*, 2009). During the AutoDock, all the water molecules were removed, the hydrogen atoms were added to the 3UPI on which atom force field charges and atom types were assigned. The ligand (phytochemicals) and the receptor protein NS5B (3UPI) were first converted from PDB format into PDBQT format by Autodock tool. To run autodock, the grid box parameter values, Kollman charges and atomic solvation parameters were added. Grid maps dimensions were set as $60 \times 60 \times 60$ points with spacing of 0.469 \AA to yield the receptor model that included atoms within 0.5 \AA of the grid centre. After Grid generation and efficient search of torsional freedom, the ligands were docked with the receptor 3UPI (NS5B). The Lamarckian genetic was used as a scoring algorithm. The number of runs for each docking experiment was set to 10. The remaining parameters were set as default. The protein-ligands docked complex was further evaluated on lowest binding energy (kcal/mol) values using the Root-mean-square-deviation data. The result of docked ligand-receptor binding interactions was visualized using the Discovery Studio 2019 client.

RESULTS AND DISCUSSION

The molecular docking is a computational tool which used to predict the binding affinity between ligands and target receptor proteins (Kumar and Doss, 2016). In the present study, druglikeness properties of all the phytochemicals were determined first and then docked with the HCV NS5B polymerase *in silico* approach. Traditional medicinal plants have also been used for treating diverse viral diseases for centuries. A number of natural phytochemicals experimentally proved that they have an antiviral activity against various kinds of viruses (Mathew *et al.*, 2014; Sangeetha and Rajarajan, 2015). Balavignesh *et al.* (2013) reported that NS5B polymerase is an RNA dependent RNA polymerase enzyme which plays an important role in replication of HCV.

The druglikeness scores of the selected ligands were analyzed using the Molinspiration tool (<http://www.molinspiration.com>) as per Lipinski's rule which determines whether particular molecule is similar to the known drugs (Lipinski *et al.*, 2012, Mishra *et al.*, 2018). It is an important parameter to determine four simple physicochemical parameter ranges ($MW \leq 500$, $\log P \leq$

Table 2. Druglikeness properties of ligands evaluated using the molinspiration tool.

Ligand name	Molecular weight (g/mol)	XLogP	Hydrogen bond donor	Hydrogen bond acceptor	Lipinski rule
Gallic acid	170.12	0.7	4	5	True
Catechin	290.271	0.4	5	6	True
Resveratrol	228.247	3.1	3	3	True
Apigenin	270.24	1.7	3	5	True
Silibinin	482.441	2.4	5	10	True
Dasabuvir	493.58	4.89	2	8	True

5, Hbond donors ≤ 5 , H-bond acceptors ≤ 10) (Arumugam *et al.*, 2012). The molecular weight of all the selected ligands was in the acceptable range (MW ≤ 500). Compounds with low molecular weight can be easily absorbed, distributed, and transported as compared to high molecular weight compounds. The XLogP value is used to assess the lipophilic efficiency that determines the potency of drug. The Molecular weight (MW), XLogP, H-bond donors, and H-bond acceptors value of all the phytochemicals were calculated and found to be within acceptable range according to Lipinski's rule (Table 2).

Table 3 revealed that the ligand binding site in the NS5B protein was predicted using the MetaPocket 2.0 on which all the five ligands confirmed the most conserved interacting amino acids of NS5B compared to the reference ligand, Dasabuvir. According

Table 3. Potential ligand binding sites in NS5B active site (3UPI) obtained from the MetaPocket 2.0.

TYR_B^38^ CYS_B^146^ VAL_B^147^ GLN_B^148^ ARG_B^154^
 LYS_B^155^ PHE_B^145^ THR_B^390^ THR_B^389^ LYS_B^491^
 ASP_B^387^ ARG_B^386^ SER_B^367^ ARG_B^394^ GLU_B^143^
 ARG_B^158^ ASP_B^352^ THR_B^364^ ARG_B^48^ ASP_B^319^
 CYS_B^366^ ASP_B^220^ PRO_B^156^ PRO_B^391^ ASN_B^411^
 ASP_B^318^ SER_B^365^ THR_B^221^ CYS_B^223^ THR_B^40^
 ALA_B^157^ ARG_B^222^ SER_B^218^ TYR_B^415^ ASN_B^316^
 SER_B^407^ SER_B^556^ GLN_B^446^ PHE_B^224^ TYR_B^219^
 SER_B^368^ LYS_B^141^ LEU_B^320^ ASN_B^369^ ARG_B^484^
 LYS_B^51^ GLY_B^351^ ASP_B^225^ VAL_B^52^ PHE_B^193^
 LEU_B^362^ GLY_B^449^ MET_B^414^ GLY_B^410^ TYR_B^448^
 ILE_B^405^ PRO_B^353^ PRO_B^354^ ASN_B^291^ LEU_B^159^
 SER_B^142^ VAL_B^144^ GLY_B^317^ ILE_B^447^ ILE_B^363^
 GLN_B^355^ SER_B^282^ THR_B^287^ SER_B^226^ TYR_B^4^
 ILE_B^160^ SER_B^288^ GLY_B^557^ GLU_B^398^ GLU_B^357^
 CYS_B^445^ ARG_B^200^ LEU_B^384^ PRO_B^197^ PHE_B^217^
 ARG_B^280^ THR_B^403^ PRO_B^404^ HIS_B^467^ TRP_B^397^
 VAL_B^161^ ALA_B^281^ ALA_B^140^ CYS_B^451^ ASP_B^559^
 ILE_B^560^ GLY_B^283^ GLY_B^558^ HIS_B^95^ PRO_B^93^
 PHE_B^162^ HIS_B^402^ MET_B^139^ TYR_B^383^ PRO_B^417^
 SER_B^96^ ALA_B^97^ ASP_B^444^ GLU_B^17^ ARG_B^168^
 ARG_B^401^ CYS_B^14^ VAL_B^201^ LYS_B^198^ TYR_B^382^
 GLU_B^18^ PRO_B^94^ PRO_B^13^ ALA_B^15^ ALA_B^16^
 ALA_B^39^ VAL_B^381^ SER_B^470^ THR_B^137^ LEU_B^474^
 SER_B^269^ LYS_B^98^ SER_B^99^ LYS_B^100^ ASP_B^164^
 PRO_B^163^ LEU_B^165^ ASP_B^135^ THR_B^136^ PHE_B^101^
 THR_B^267^ ILE_B^134^ VAL_B^167^ HIS_B^118^ VAL_B^122^
 ASP_B^125^ ARG_B^259^ LEU_B^126^ PRO_B^350^ PRO_B^356^
 ILE_B^11^ THR_B^12^ THR_B^41^ SER_B^42^ ASN_B^268^
 GLY_B^271^ LYS_B^270^ SER_B^19^ PRO_B^133^ THR_B^292^
 CYS_B^289^ TYR_B^555^ VAL_B^284^ SER_B^121^ GLY_B^554^
 ALA_B^450^ TYR_B^561^

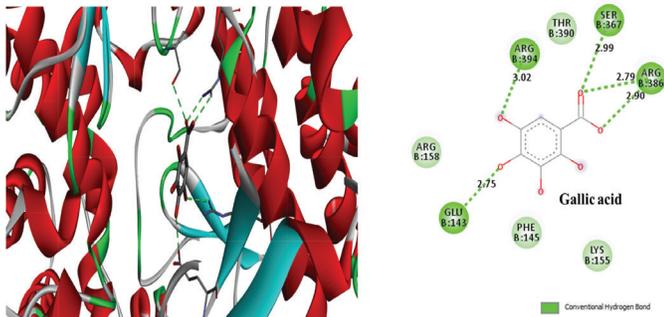
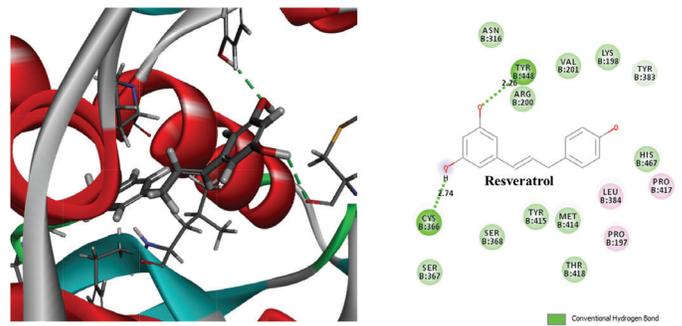
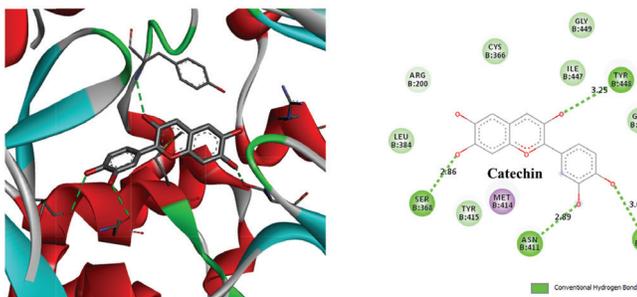
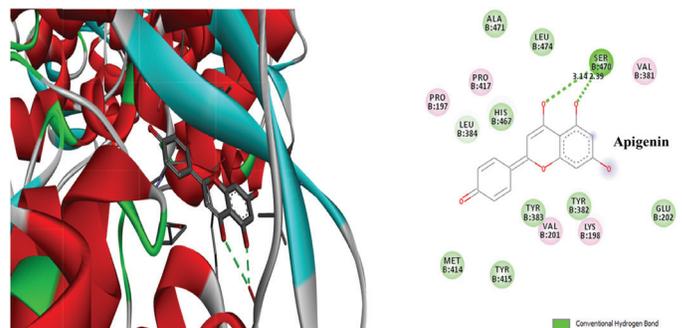
to the Huang and Schroeder (2008), protein binding site prediction helps to improve protein docking. The present study revealed that there are 14 interactive amino acids residues involved between the NS5B receptor protein and the ligands. These interacting residues include GLU B:143, SER B:367, ARG B:386, ARG B:394, SER B:368, ASN B:411, SER B:407, TYR B:448, CYS B:366, SER B:470, LEU B: 384 ASN B:316, PRO B:197, and LEU B:384 constituting the potential binding active site for the HCV-NS5B. The docking score, binding amino acid residues, H-bond distance (Å), and number of hydrogen bonds are given in Table 4. All the ligands were interacted with the type B polypeptide chain of NS5B which was used in the docking study.

Figure 2 depicted the docking complex between the Gallic acid and the NS5B. Gallic acid formed five H-bonds with the residues of NS5B, include GLU143, SER367, and ARG386. The docking score was -5.48 kcal/mol. Figure 3 showed the binding relationship between the catechin and the NS5B with the binding energy -7.31 kcal/mol. It makes four hydrogen bonds with the amino acids SER368, SER407, TYR448, and ASN411 in the binding pocket of NS5B active site. The docked resveratrol-NS5B protein complex is formed two hydrogen bonding with the amino residues TYR448, CYS 366 of the NS5B as shown in the Figure 4. It has binding energy -8.14 kJ/mol. Figure 5 exhibited the hydrogen bonding interactions between the Apigenin and the NS5B which docks one amino acid SER 470 at NS5B active site and its docking score was -8.75 kcal/mol. Figure 6 demonstrates the docking complex between the silibinin and the NS5B with the binding energy -10.57 kcal/mol. This docking showed three H-bond interactions with the amino acid residues: LEU384 and ASN316 at NS5B binding site. The reference ligand, dasabuvir showed high docking score -11.43 kcal/mol and bound to the residue PRO197 and LEU384 of NS5B binding site via three H-bonds (Fig. 7). The binding energies of all the ligands phytochemical compounds were compared to the reference ligand (Dasabuvir). Therefore, these results demonstrated that there are good binding interactions between phytochemicals and NS5B polymerase. Based on minimum docking score, the most active ligands with the NS5B are catechin (-7.31 kcal/mol), resveratrol (-8.14 kcal/mol), apigenin (-8.75 kcal/mol), and silibinin (-10.57 kcal/mol) compared to the gallic acid (-5.48 kcal/mol). Therefore, these results suggested that silibinin has best binding score compared to other docked phytochemicals score compared to other docked ligands. With this good docking score, silibinin was proved to be most active compounds which may possess antihepatitis activity against HCV similar to the docked dasabuvir because both have hydrogen binding interactions with the LEU384 residues of NS5B active site. Silibinin has been tested against HCV and its antiviral effect was found to be effective in inhibiting the enzymatic activity of NS5B RNA-dependent RNA polymerase (Usman and Sobia, 2014). Our findings are also supported the antiviral effect of silibinin.

Kortemme *et al.* (2003) demonstrated that minimum the binding energy, greater is the binding affinity in silico study. *In silico* study also suggested that greater the hydrogen bond interactions between the enzyme (receptor protein) and ligand determines the

Table 4. Molecular docking analysis of ligands against NS5B polymerase (3UPI).

Ligands	Docking score(kcal/mol)	Binding residues	H-bond distance (Å)	Number of hydrogen bonds
Gallic acid	-5.48	GLU B:143	2.75	5
		SER B:367	2.99	
		ARG B:386	2.79, 2.90	
		ARG B:394	3.02	
		SER B:368	2.86	
Catechin	-7.31	ASN B:411	2.89	4
		SER B:407	3.02	
		TYR B:448	3.25	
Resveratrol	-8.14	TYR B:448	2.26	2
Apigenin	-8.75	CYS B:366	2.74	2
Silibinin	-10.57	SER B:470	3.14, 2.39	2
		LEU B:384	2.39, 2.79	
Dasabuvir (reference ligand)	-11.43	ASN B:316	2.73	3
		PRO B:197	2.69, 2.75	
		LEU B:384	2.78	

**Figure 2.** Three-dimensional and two-dimensional interactions of Gallic acid against the active site of NS5B polymerase.**Figure 4.** Three-dimensional and two-dimensional interactions of Resveratrol against the active site of NS5B polymerase.**Figure 3.** Three-dimensional and two-dimensional interactions of Catechin against the active site of NS5B polymerase.**Figure 5.** Three-dimensional and two-dimensional interactions of Apigenin against the active site of NS5B polymerase.

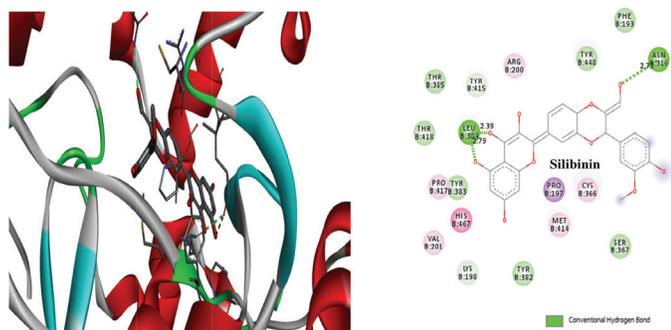


Figure 6. Three-dimensional and two-dimensional interactions of Silibinin against the active site of NS5B polymerase.

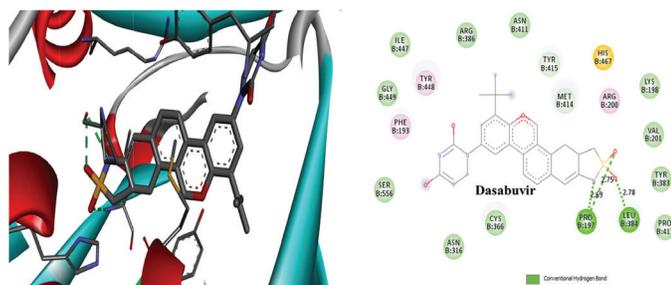


Figure 7. Three-dimensional and two-dimensional interactions of Dasabuvir against the active site of NS5B polymerase.

strength of binding (Biswal *et al.*, 2019). Elfiky (2019) reported that docking calculations are used to predict the binding affinity of the compounds to HCV NS5B active site (Kumar and Doss, 2017). The active functional group of phytochemicals are completely surrounded by the binding pocket of the NS5B because they fit properly into its active site via hydrogen bonding interactions (Jin *et al.*, 2014). From the results of Docking analysis, it was found that all phytochemicals have antiviral inhibitory activity against HCV NS5B polymerase enzyme.

CONCLUSION

This study suggested that all the phytochemical compounds could be potent HCV NS5B inhibitors which might be due to their good binding efficacy with the HCV NS5B which may further investigate *in vitro* and *in vivo* model.

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CONFLICT OF INTEREST

The author confirms no conflict of interest for this manuscript.

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