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Short Communication

ANTI NS3 HCV ACTIVITY OF *BOERHAVIA DIFFUSA* L.: AN *IN SILICO* ANALYSIS

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ABSTRACT

Objective: The present study focuses on the inhibition of NS3 HCV protease there by blocking replication of the HCV inside the hepatocytes.

Methods: Docking was carried out to evaluate the inhibitory potential of bioactive compounds in *B. diffusa* against HCV NS3 protease by using Discovery studio 4.0.

Results: Phthalic acid, caffeoyltartaric acid, propionic acid, quercetin, 3,5,7,2,5 penta hydroxyl flavones, silanamine and beta-sitosterol significantly bind with HCV NS3 protease with good binding energies. All these compounds passed Lipinskis rule of five and ADME/T.

Conclusion: The *in silico* analyses establishes that active principle present in *B. diffusa* to inhibit viral replication.

Keywords: Hepatitis C virus (HCV), NS3 protease, *Boerhavia diffusa, In silico* analysis, Lipinskis rule

Hepatitis C virus (HCV) is the main cause of chronic liver disease worldwide as well as the primary indication for liver transplantation [1]. The consequences of infection are often intense since the liver is the most important organs in the body. There is a great demand for a drug that acts directly on HCV preferably oral, to provide hepatitis C patients more effective treatments with fewer side effects. HCV NS3 serine protease is the most intensively studied anti-HCV target, possibly because it plays a vital role in viral replication [2].

Computational methods give a more accurate estimation of interactions between the lead compounds and their targets and help in facilitating rational drug design. *Boerhavia diffusa* belongs to the family Nyctaginaceae, was selected for the present investigation [3].

The three dimensional structure of NS3 HCV protease was retrieved from the Protein Data Bank (PDB) (http://www.pdb.org/) with PDB ID 3knx. The NMR structure of this protein was prepared using 'prepare protein' option in Discovery studio 4.0. The protein was prepared by removing crystallographic water molecules and heteroatoms. Hydrogen atoms were added to correct the chemistry of protein. Energy minimization was performed and this minimized structure was used as the receptor for the docking studies.

Extensive literature survey was performed to find out the active phytochemicals with pharmacological activity present in *B. diffusa* [4]. The structures of the ligands were downloaded in. sdf format from the PubChem database (http://pubchem.ncbi.nlm.nih.gov/). Preparation of the ligands was carried out by energy optimization and adding hydrogen atoms. The drug likeliness of the selected active phytochemicals was analyzed using Lipinski's and Verber rules [5]. ADMET values were predicted for ligands using ADMET descriptors in Discovery studio 4.0. Toxicity profiles of the ligands were done by utilizing TOPKAT which uses a range of Quantitative Structure Toxicity Relationship (QSTR) in Discovery studio version 4.0.

The interaction study was conducted in Ligandfit Accelrys Discovery Studio Software 4.0. The binding sites of the protein were predicted using 'find cavities' from the receptor site parameter of the tool. Using libdock module, libdock procedure was applied to position conformation of the ligand correctly in the active site. The binding results could be displayed by scoring ligand poses and several scoring functions were used for measuring the goodness of docking, to find the top ranked pose for ligands [6].

Molecular docking is considered as an important technique in drug designing and screening for novel inhibitors against this dreadful and challenging diseases. Hepatitis C is an appalling disease and requires urgent attention to developing new inhibitory compounds. The potential of fifty three ligands selected from *B. diffusa* were used for the interaction against HCV NS3 protease. Screening of these ligands was done by using 'Lipinski's and Verber rule. The Lipinski values of 36 ligands were within the limits of druggability (table 2).

The ligands were docked with the catalytic triad of HCV NS3 protease to assess their affinity as inhibitors. NS3 HCV protease (3knx) interacted with 7 out of 36 ligands in *B. diffusa.*

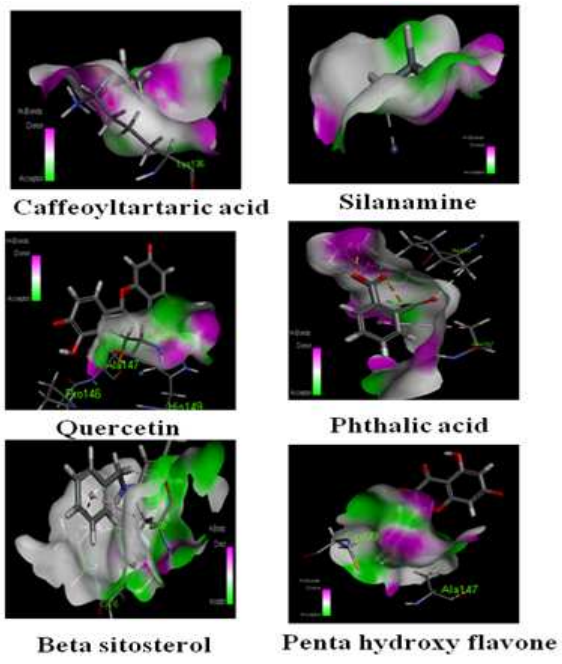

Fig. 1: Docked phytochemicals complexes with the binding pocket of HCV NS3 protease

Table 1: Docking results of ligands with NS3 HCV protease

S. No.	Name of the compound	C Docker energy	Binding energy	Pose No:	No: H_2 bonds	Hydrogen bond interaction	Aminoacid residues
1	Phthalic acid	21.78	-290.5968	1	3	A: Lys 136:HZ3-1017:O2 A: Lys 136:NZ-1017:O1 A: Lys 136:HZ2-1017:O4 A: Ile 136:HA-1017:O3	Lys 136 Ile 136 Ala 150
2	Caffeoyl tartaric acid	30.8667	-246.9364	43	5	A: Arg 62:NH1-9857913:O_4 B: Lys20:NZ-9857913:O_4 A: Arg 62:HE-9857913:O_4 B: Lys 20:HT2-9857913:O_3 B: Gly 21:HN-9857913:O_4 B: Lys 20:HA-9857913:O_4 9857913-A: Ile 17 9857913-A: Ala 39	Arg 62 Lys20 Gly 21 Ile 17 Ala 39
3	Propionic acid	22.6645	-172.4525	2	3	A: Lys 136:HZ3-6581:O1 A: Lys 136:HZ2-6581:O2 A: Lys 136:HE1-6581:O1	Lys 136
4	Quercetin	25.2038	-97.3736	1	1	A: ZN 90:ZN-5280343:O2-ES A: Pro 146: HD-5280343:O6 5280343:O2-A: His 149 A: Cys 99: SG-5280343 5280343-A: Ala 147 5280343-A: Cys 99 5280343-A: Ala 147	Pro 146 His 149 Cys 99 Ala 147
5	Penta hydroxy flavones	10.6412	-94.7913	4	1	44258716:H30-A: Cys99:SG A: Cys99: SG-44258716 44258716-A: Ala 147	Cys99 Ala 147
6	Silanamine	15.0446	-50.3675	6	1	14094712:H6-A: Arg 155:O	Arg 155
7	β Sitosterol	13.8994	-21.8079	9	1	222282:H18-A: Ala 39:O 222282:C10-A: Lue13 222282:C10-A: Cys 16 222282:C10-A: Ile 117 222282:H18-A: Leu 13 222282:H18-A: Ile 117 222282:H18-A: Ala 39	Ala 39 Lue13 Cys 16 Ile 117

Table 2: ADMET properties of the selected ligands

S. No.	Name of the compound	Pubchem ID	Solubility	BBB	Absorption	Log P
1	Phthalic acid	1017	4	3	0	1.089
2	Silanamine	14094712	4	2	0	0.612
3	β sitosterol	222282	2	0	0	4.194
4	Pentahydroxy flavone	44258716	3	4	1	1.63
5	Quercetin	5280343	3	4	1	1.63
6	Propionic acid	6581	4	3	0	0.493
7	Caffeoyl tartaric acid	9857913	4	4	3	0.363

Solubility:-0-extremly low; 1-very low; 2-good; 3-slightly soluble; 4-optimal; 5 very soluble, Blood brain barrier penetration:-0-very high; 1-high; 2-medium; 3-low; 4-undefined, Human intestinal absorption:-0-good; 1-moderate; 2-low; 3-very low Log p<5

This study has discovered the potential binding of ligands like phthalic acid, caffeoyltartaric acid, propionic acid, quercetin, 3, 5, 7, 2, 5 penta hydroxyl flavones, silanamine and beta-sitosterol with NS3 HCV. Docking results are illustrated in table 1 and fig. 1. The compounds which interacted well with the protein include flavonoids like quercetin and 3, 5, 7, 2, 5 penta hydroxyl flavones.

Non flavonoid phenolic compound caffeoyltartaric acid interacted well with NS3 protease with-246.93 binding energy. Phthalic acid and caffeoyltartaric acid exhibited high CDOCKER energy of 21.78 and 30.86 Kcal/mol respectively. A number of reports confirm the role of flavonoids in inhibition of HCV replication through diverse mechanisms.

CONCLUSION

HCV infection is a major global health problem necessitating effective treatment. The current interferon treatment is costly, with significant side effects and fails to cure about half of all infections. Thus there is a need to develop anti HCV agents from plants already in use, which is less toxic, more efficacious and cost effective. Seven lead compounds obtained from *B. diffusa* interacted with NS3 HCV protease. Inhibition of NS3 protease by these phytochemicals might affect proteolytic processing of HCV polyprotein and inhibit viral RNA dependent RNA polymerase, thereby suppressing HCV RNA levels. They are strong candidates for the development of potentially beneficial anti HCV drugs by functionally regulating its replication.

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CONFLICT OF INTERESTS

Declared none

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