IJPSR (2013), Vol. 4, Issue 1 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 10 September, 2012; received in revised form, 11 November, 2012; accepted, 22 December, 2012

MOLECULAR DOCKING STUDIES OF PHYTOCHEMICAL COMPOUNDS WITH VIRAL PROTEASES

Rajarajeshwari Ramaiah and P. Chitra Suresh

Department of Bioinformatics, Sri Ramakrishna College of Arts & Science for Women, Coimbatore, Tamil Nadu, India

Keywords:

Viral proteases, Phytochemical compounds, Biological activity, Molecular docking

Correspondence to Author:

Rajarajeshwari Ramaiah

Department of Bioinformatics, Sri Ramakrishna College of Arts & Science for Women, Coimbatore, Tamil Nadu, India

E-mail: rajeebioinfo@yahoo.com

QUICK RESPONSE CODE

IJPSR: ICV- 5.07

Website: www.ijpsr.com

ABSTRACT

Viruses are the major pathogenic agents that can cause variety of diseases in humans, animals and plants. Several deadly diseases like Hepatitis A, Hepatitis C, encephalitis, meningitis, and influenza are caused by viruses. Due to the constant and rapid emergence of viral pathogens, current recommended commercial drugs for above diseases are becoming resistant. In this view in present study forty three medicinal plants with numerous phytochemicals present in Dukes phytochemical database are subjected to PASS (Prediction of Activity Spectra for Substances) server for the prediction of their biological activity. Compounds with maximum probable activity for inhibiting specific viral targets are chosen and their drug likeliness is estimated based on Lipinski's rule of five. The medicinal value of those compounds and its activity for inhibiting specific viral targets are analyzed from the PASS prediction results. Several interesting properties of Influenza virus, Arbovirus, Picornavirus, Flavivirus, and Herpes virus proteases with catalytic dyad and triad, active site, three dimensional structural features and their role in disease progression are review from the literature. Further molecular docking studies has been carried out using the commercial software Schrödinger USA.

INTRODUCTION: The Arthropod borne viruses such as sindbis virus, Chikungunya virus, Eastern, Western and Venezuelan equine encephalitis virus, Ross River Virus belonging to the family Togaviridae and Dengue virus, West Nile virus belonging to the family Flaviviridae and Herpes virus belonging to the family Herpesviridae cause severe hemorrhagic fever, encephalitis and meningitis [1, 2]**.** These viruses are transmitted through arthropod vectors such as *Aedes aegypti, Aedes Albopictus, Aedes Vexans, Aedes Chrysolineatus, Aedes niveus, and Aedes vitattus* [3]**.** Hepatitis the inflammation of liver which is caused by Hepatitis A virus belonging to the genus Picornavirus and Hepatitis C Virus belonging to the genus Flavivirus are the leading cause of liver Cirrhosis and hepatocellular carcinoma [4]**.**

H1N1 influenza virus belonging to the family orthomyxoviridae is the causative agent of seasonal flu and the genes in this new virus were very similar to those found in pigs in North America [5]**.** Owing to the undesirable side effects of the current recommended medicines for treating Viral influenza, Hepatitis, meningitis and encephalitis, there is a need for selective and effective inhibitors for preventing the above viral diseases.

The commercially available drugs like amantadine, rimantatine, oseltamivir and Zanamavir for treating influenza are associated with the side effects of central nervous system and gastrointestinal tract. Oseltamivir resistant H1N1 viruses spontaneously arose and spread globally.

Currently circulating resistant H1N1 viruses carry the histidine- to-tyrosine (His274Tyr) substitution in neuraminidase that confers resistance to oseltamivir but does not affect susceptibility to zanamivir [6].

Hepatitis A and C Viruses is the major causative agent of chronic hepatitis and the only available treatment is Ribavirin in combination with pegylated apha interferon which remains ineffective for treating the disease. The side effects of the interferon therapy are associated with Haemolytic anaemia, Interstitional pneumonitis and thyroid dysfunction [7]. The drugs namely Acyclovir and Valacyclovir are currently used for treating Herpes virus infection [8].

Chloroquine was first reported to inhibit sindbis virus and Semliki forest virus infection. The antimalarial drug quinine appears to be a more likely candidate for antiviral therapy against chikungunya virus and sindbis virus. Recent studies on the carbocyclic analogue of cytidine (cyclopentylcytosine or carbodine) suggest that it has potential as an antiviral agent against Venezuelan Equine Encephalitis Virus. How ever, new approaches involving natural products of plants provide the stimulus for improving development of antiviral candidates [9].

In this view, in the present study, forty three medicinal plants with numerous phytochemicals present in Dukes phytochemical database are subjected to PASS (Prediction of Activity Spectra for Substances) server for the prediction of their biological activity. Compounds with maximum probable activity for inhibiting specific viral targets are chosen and their drug likeliness is estimated based on Lipinski's rule of five. The medicinal value of those compounds and its activity for inhibiting specific viral targets are analyzed from the PASS prediction results.

By analyzing the biological activity of the phytochemical compounds, the target proteins involved in the process of viral replication and disease progression are reviewed from the literature. The non-structural proteins are responsible for replication and packaging of the viral genome into capsids formed of structural proteins. Since the vast majority of today's antiviral drugs exert their actions through enzymes involved in viral replication, much attention has focused on studying the non-structural proteins [10].

The viral proteases of non-structural polyprotein are the attractive targets for antiviral drug design since proteases play initial role in viral replication and propagation by cleaving the replication complex. Proteases, commonly called peptidases, represent approximately 2% of the total number of proteins present in all types of organisms. Many of these enzymes are of medical importance, and are potential drug targets as they originate from the genome of the disease-causing micro organisms [10].

The single stranded RNA genome of viruses belonging to the family Togaviridae and Flaviviridae are composed of two long open reading frames, the first of it at the 5' region of the genome encodes four nonstructural proteins (nsp1234), and the 3' region encodes the three major structural proteins (the capsid and two envelope proteins) . The polyproteins are auto-catalytically cleaved into four nonstructural proteins (nsP1, nsP2, nsP3, nsP4) by nsP2- associated protease activity [11].

The viral proteases exhibits catalytic triad formed by three amino acids which plays very important role in cleaving the polyproteins. By binding the protease catalytic site with the design of new inhibitors, the residues involved in catalysis are arrested and so cleavage of polyprotein is terminated and thereby viral replication can be prevented. Hence Proteases are chosen as propitious target for the design of antiviral drugs.

In present study, to explore the binding mechanism of phytochemicals, molecular docking studies have been performed with the target proteins. The target proteins chosen are neuraminidase for H1N1 influenza and nsp2 protease for Hepatitis A and C viruses, Herpes and Sindbis Virus infection.

The X-ray crystal structure of Zanamivir in complex with neuraminidase (PDB ID: 3CKZ), Hepatits A virus proteinase (PDB ID: 1HAV), Herpes virus protease (PDB ID: 1AT3), and HCV Protease (PDB ID: 1JXP) were retrieved from the Protein Data Bank. Due to the lack of crystal structure of Sindbis virus protease, the structure has been modeled by employing multi-template modeling technique with the templates of nsp2 protease from Venezuelan Equine Encephalitis Virus and Chikungunya virus proteins.

The protein targets are docked with the phytochemical compounds and the results were compared with the commercially available drugs for treating the influenza, Hepatitis, meningitis and encephalitis. The active site of the target neuraminidase was defined by generating the grid box of dimension 20Å around the co-crystal drug Zanamavir.

For all other targets the active site was defined around the catalytic triad forming residues namely Serine, Histidine, Aspartic acid for serine protease family of proteases (Hepatitis A, Hepatitis C, Herpes Virus) and Cysteine, Histidine, Aspartic acid for cysteine protease family of protease (Sindbis Virus). Molecular docking studies have been performed on the Red hat Linux EL work station using the commercial software Schrödinger USA.

MATERIALS AND METHODS:

Collection of Inhibitors: Two types of inhibitors belonging to different category viz, Commercial drugs, and Phytochemical compounds were chosen for the present study.

Commercial drugs: The commercial drugs for Sindbis Virus infection namely Carbodine, Chloroquine, and Quinine, Hepatitis namely Ribavirin, drugs for Herpes virus infection namely Acyclovir and Valacyclovir, and anti-influenza drugs like Zanamavir and Oseltamivir were collected from drug bank.

Phytochemical Compounds: The phytochemical compounds present in the forty four plants namely *Origanum vulgare, Allium Sativum, Allium cepa, Aloe vera, Frangula alnus, Ginkgo biloba, Fragaria* spp *Glycine max, Teucrium chamaedrys, Plantago major, Arbutus unedo, Glechoma hederacea, Leonurus cardiaca, Myroxylon balsamum, Eucalyptus globules, Allium sativum, Citrus aurantium, Citrus limon, Curcuma longa, Daucus carota, Arachis hypogaea, Camellia sinensis, Cuminum cyminum, Mangifera indica, Arctostaphylos uva-ursi, Crataegus laevigata, Pterocarpus santalinus, Hypericum perforatum, Catha edulis, Vitis vinifera, Plantago major, Glycyrrhiza glabra, Citrus paradisi, Myroxylon balsamum, Juglans cinerea, Juglans nigra, Juglans regia,Teucrium polium, Arbutus unedo, Cuscuta reflexa, Nicotiana tabacum, Acacia nilotica, Acacia catechu, Polygala penaea* were collected from Phytochem DB. The 2-D dimensional structures were collected from pubchem database. PhytochemDB mainly contains phytochemical compounds of the plants.

It also contains data information about the chemical composition of plants. This database currently contains phytochemicals, taxonomic and ethnobotanical data. The search is available on chemical name, family, genus system. (http://ukcrop.net/perl/ace/search /PhytochemDB). Seventy five phytochemical compounds from the above plants were collected from this database.

Prediction of activity: The biological activity spectra for the collected compounds were predicted by the application of the program PASS (Prediction of Activity Spectra for Substances). The program generates the most probable activities and in activities, for a given compound which are characterized by *Pa* values close to 1, and *Pi* values close to 0. (http://pharmaexpert.ru/ passonline).

Targets for Drug Design: Five different viral proteins namely neuraminidase and nsp2 protease of Hepatitis A (Picornavirus) and Hepatitis C (Flavivirus), Herpes Virus and Sindbis Virus (alphavirus) has been chosen as targets for the present study.

Sinbis Virus Protease: The modeled structure of Sindbis virus protease was deposited at Protein Model Portal with (PMID: PM0077739) is formed by catalytic Cys11 and His88. The active site residues with respect to VEEV protease are Asn9, Val1and Pro44 form the S1 binding site. The S2 site consist of Trp89 and the S3 binding site is formed by the residue Alanine and threonine at the position 241 and 245

Hepatitis A Virus protease (PDB ID: 1HAV): Crystal structure of Hepatits A Virus protease belonging to the family picornaviridae was taken from Protein Data Bank as target molecule (PDB ID:1HAV) with 2Å resolution for docking studies. The active-site and substrate-binding regions are located in a surface groove between the two domains. The catalytic triad of Hepatitis A virus protease is formed by the three residues Cys172, His44 and Asp84 [12].

Hepatitis C Virus Protease: Crystal structure of Hepatitis C Virus NS3-4A protease belonging to the family flaviviridae was taken from Protein Data Bank as target molecule (PDB ID: IJXP) with 2.2Å resolution for docking studies. The catalytic triad is located in a cleft between two sub-domains, with His57 and Asp81 in the N-terminal sub-domain and Ser139 in the C-terminal one which is activated by NS4A cofactor [13].

Herpes Virus protease: Crystal structure of Herpes Virus protease belonging to the family Herpesviridae was taken from PDB (Protein Data Bank) as target molecule (PDB ID: IAT3) with 2.5 Å resolution for docking studies. The three dimensional structures of the herpesvirus proteases show that, in addition to the active site serine, conserved His63 and His148 (HCMV numbering) are in the active site, with His63 positioned for hydrogen bonding to the nucleophilic serine [14]. The X-ray structure of Herpes virus protease 1AT3 reveals HIS61, HIS148, SER129 forms catalytic triad of herpes virus protease.

N1 Neuraminidase: Crystal structure of N1 neuraminidase was taken from PDB (Protein Data Bank) as target molecule (PDB ID: 3CKZ) with 1.9 Å resolution for docking studies. The active site of N1 Neuraminidase is defined by the Arg118, Arg152, Arg292 and Arg371, Arg224 and Glu276. The replication of virus particles is blocked by the application of NA inhibitors, which have the ability to fit into the active site of the enzyme and avoid the cleavage of the connection between host cell and newly built virions [6].

Molecular docking: All computational work has been performed using the Red hat Linux EL workstation with the molecular modeling software Schrödinger USA. Glide extra precision mode of docking was chosen and the best docked conformation as maestro format was imported on the workspace and exported as PDB format. The hydrogen bonding interaction between the receptor and the ligand was visualized using the software PYMOL.

RESULTS:

TABLE 1: RESULTS FROM PASS SERVER-PREDICTION OF BIOLOGICAL ACTIVITY

S. NO.	Compound Name	Source Plant	PUBCHEM ID	Antiviral Activity Specific to particular Virus	Probable Activity	Probable Inactivity
1	Oleanolic acid	*Origanum vulgare*	10494	Influenza Virus	0.91	0.002
2	Curcumin	*Curcuma longa*	969516	Picornavirus	0.525	0.084
3	Bilobetin	*Ginkgo biloba*	5315459	Herpes Virus	0.543	0.017
4	Rutin	*Origanum vulgare*	5280805	Hepatic disorders treatment	0.638	0.014
5	Juglone	*Juglans cinerea* *Juglans nigra* *Juglans regia*	3806	Arbovirus	0.677	0.053

TABLE 2: DRUG LIKENESS BASED ON LIPINSKI'S RULE OF FIVE

S. NO.	Compound Name	Molecular weight g/mol	H-Bond Donor	H-Bond acceptor	QP Log(po/w)
1	Oleanolic acid	456.70	2	3	7.5
2	Curcumin	368.37	2	6	3.2
3	Bilobetin	**552.48**	5	10	5.4
4	Rutin	**610.51**	**10**	**16**	1.3
5	Juglone	174.15	1	3	1.9

TABLE 3: TARGETS FOR SPECIFIC VIRAL DISEASES

S. NO.	Disease	Viral targets	Family	PDB ID
1	Influenza	Neuraminidase		3CKZ
2	Hepatitis A	Hepatitis A Virus Proteinase	picornavirus	1HAV
3	Chickenpox, shingles, and postherpetic neuralgia	Herpes virus protease	Herspes viridae	1AT3
4	Hepatitis C	HCV Protease	Flavivviridae	1JXP
5	Encephalitis and meningitis	Sindbis virus protease	Arbovirus belonging to togaviridae	Modeled structure

TABLE 4: MOLECULAR DOCKING RESULTS OF THE PHYTOCHEMICAL AGAINST THE SELECTED TARGETS

Compound Name	Target	H-Bond	Distance Å	Glide Score	Glide Energy (Kcal/mol)
Oleanolic acid	Neuraminidase	(ARG371)N H…O (ARG292)N-H…O (TYR347)O-H…O	3.2 3.3 3.3	-5.4	-40.02
Curcumin	Hepatitis A Virus protease	O-H...O(VAL144) O-H...O(HIS44)	2.8 2.9	-8.8	-56.92
Bilobetin	Herpes Virus Protease	O-H...O(ASP60) N-H...O(ARG156) (THR132)N-H...O	3.2 2.8 2.7	-5.9	-35.4
Rutin	Hepatitis C Protease	(ARG155)N-H...O (ALA157)N-H...O (HIS57)N-H...O	3.3 3.3 2.6	-7.9	-54.9
Juglone	Sinndbis Virus protease	(TRP89)N-H...O O-H...O(HIS45) (ARG248)N-H…O	2.6 3.1 2.9	-7.6	-54.96

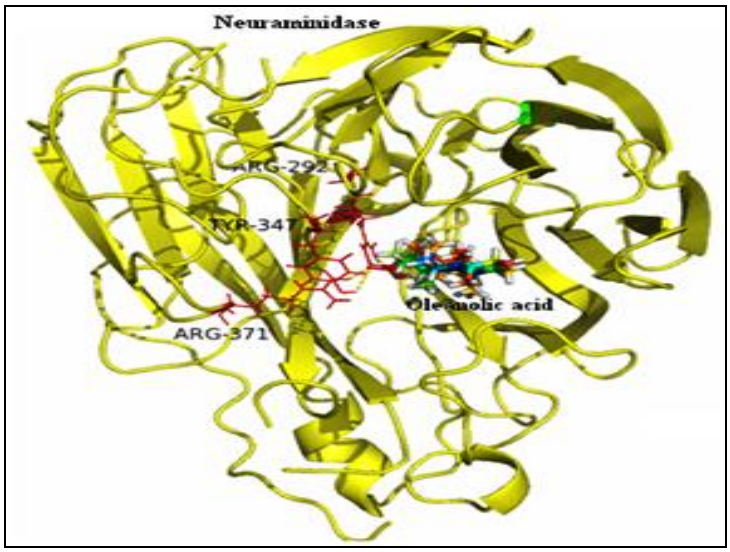

FIGURE 1: DOCKED SITE OF OLEANOLIC ACID WITH THE TARGET NEURAMINIDASE

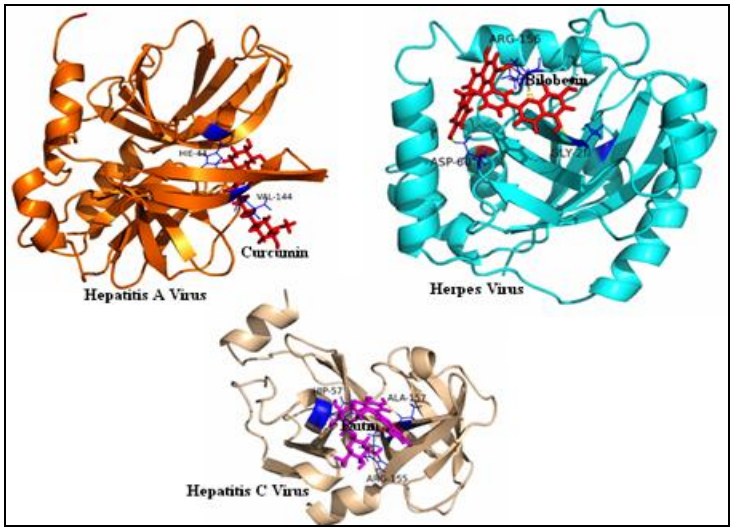

FIGURE 2: DOCKED SITE OF CURCUMIN, BILOBETIN AND RUTIN AT THE ACTIVE POCKET OF PROTEASE TARGETS OF HEPATITIS A, C AND HERPES VIRUS

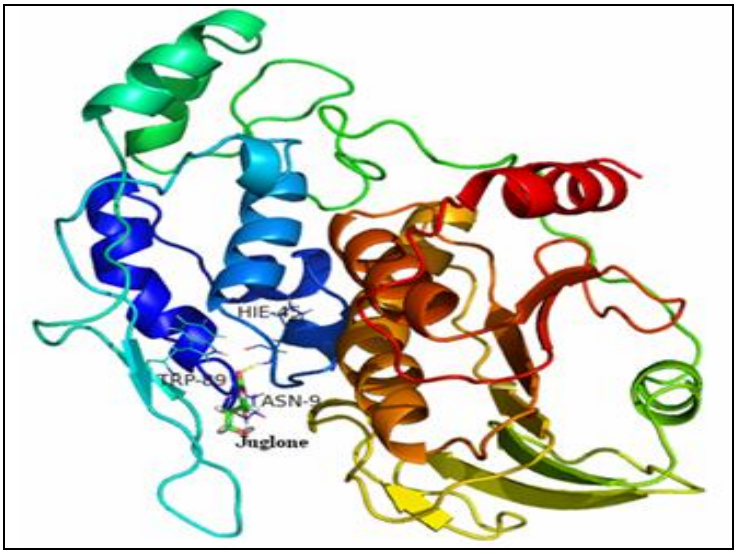

FIGURE 3: DOCKED SITE OF JUGLONE AT THE ACTIVE SITE OF SINDBIS VIRUS PROTEASE

TABLE 5: XP RESULTS FOR COMMERCIALS DRUGS AGAINST THE SELECTED TARGETS

S. NO.	TARGETS	Commercial drugs	Glide Score	Glide Energy
1	Neuraminidase	Oseltamivir	-5.5	-36.31
		Zanamivir	-4.9	-32.42
2	Hepatitis A Virus and C Virus protease	Boceprevir	-4.1	-39.52
		Ribavirin	-5.7	-47.42
		Telaprevir	-5.2	-45.21
3	Herpes Virus Protease	Aciclovir	-4.0	-31.48
		Valaciclovir	-3.7	-27.63
		Penciclovir	-3.4	-27.20
		Ganciclovir	-2.8	-27.84
4	Sindbis Virus Protease	Chloroquine	-5.4	-36.11
		Quinine	-5.2	-31.57
		Carbodine	-6.9	-32.24

TABLE 6: HYDROGEN BONDING INTERACTIONS OF THE TARGETS WITH THE BEST DRUGS FROM DRUG BANK

S. NO.	Drug Name	H-Bond	Distance Å
1	Oseltamivir	(ARG156)N-H...O	2.9
		N-H...O(GLU119)	2.8
		(ARG371)N-H...O	3.4
		(TYR347)O-H...O	2.9
		(ARG292)N-H...O	3.0
2	Ribavirin	O-H…O(GLU291)	2.8
		O-H…O(GLU291)	2.7
		(ASN229)N-H…O	2.8
		(GLY209)N-H…O	3.1
		(GLY207)N-H…O	3.0
3	Aciclovir	O-H…O(ASP60)	3.1
		N-H…O(ARG156)	2.9
4	Chloroquine	(TRP89)N-H...O	2.6
		(HIS45)N-H...O	3.2
		O-H...O(PHE209)	2.9

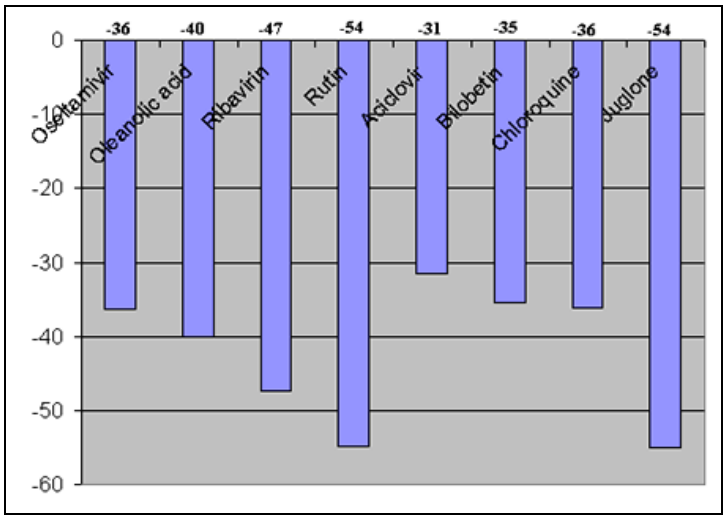

FIGURE 4: COMPARISON OF DOCKING ENERGY OF THE COMMERCIAL DRUGS WITH THE PHYTOCHEMICAL COMPOUNDS

DISCUSSION: Viruses are the major pathogenic agents that can cause variety of diseases in humans, animals and plants. Several deadly diseases like Hepatitis A, Hepatitis C, encephalitis, meningitis, and Influenza are caused by viruses. Due to the constant and rapid emergence of viral pathogens current recommended commercial drugs for above diseases are becoming resistant.

In this view, in the present study, forty three medicinal plants viz., *Origanum vulgare, Allium Sativum, Allium cepa, Aloe vera, Frangula alnus, Ginkgo biloba, Fragaria spp., Glycine max, Teucrium chamaedrys, Plantago major, Arbutus unedo, Glechoma hederacea, Leonurus cardiaca, Myroxylon balsamum, Eucalyptus globules, Allium sativum, Citrus aurantium, Citrus limon, Curcuma longa, Daucus carota, Arachis hypogaea, Camellia sinensis, Cuminum cyminum, Mangifera indica, Arctostaphylos uva-ursi, Crataegus laevigata, Pterocarpus santalinus, Hypericum perforatum, Catha edulis, Vitis vinifera, Plantago major, Glycyrrhiza glabra, Citrus paradisi, Myroxylon balsamum, Juglans cinerea, Juglans nigra, Juglans regia, Teucrium polium, Arbutus unedo, Cuscuta reflexa, Nicotiana tabacum, Acacia nilotica, Acacia catechu, Polygala penaea* with numerous phyto-chemicals present in Dukes phytochemical database are subjected to PASS server for the prediction of their biological activity (**Table 1**).

Compounds with maximum probable activity for inhibiting specific viral targets are chosen and their drug likeliness is estimated based on Lipinski's rule of five (**Table 2**). The medicinal value of those compounds and its activity for inhibiting specific viral targets are analyzed from the PASS prediction results.

The three dimensional structures of the phytochemical compounds was retrieved from PUBCHEM database as SDF files and converted to .MOL files using Web lab viewer.

Molecular docking studies of the above viral targets namely N1 Neuraminidase, Hepatitis A Virus proteinase, Herpes virus protease, Hepatitis C Virus protease and Sindbis Virus protease has been performed with the compounds from Dukes database using the commercial software Schrödinger USA (**Table 3**).

The active site of the target neuraminidase was defined by generating the grid box of dimension 20Å around the co-crystal drug Zanamavir. For all other targets the active site was defined around the catalytic triad forming residues namely Serine, Histidine, Aspartic acid for serine protease family of proteases (Hepatitis A, Hepatitis C, Herpes Virus) and Cysteine, Histidine, Aspartic acid for cysteine protease family of protease (Sindbis Virus). The three dimensional structures of the target proteins Neuraminidase (3CKZ), Hepatitis A Virus Proteinase (1HAV), Herpes virus protease (1AT3), HCV Protease (1JXP) were retrieved from the Protein Data Bank.

Owing to the lack of three dimensional structure of Sindbis Virus protease, multi template modeling technique has been employed for modeling the target protein sequence with the templates Venezuelan equine encephalitis Virus protease (2HWK) and Chikungunya Virus protease (3TRK). Further the structure was validated and refined using PROCHECK available in Structure Analysis and Verification Server.

All five target proteins were prepared using Schrodingers comprehensive protein preparation wizard in order to correct the Bond angles and Bond length between one amino acid and the other amino acid. Similarly all seventy four ligands were prepared using ligprep module in GLIDE. After defining the active site for each target separately the target protein file and the ligand file are given as input for the GLIDE program and the docking calculations are performed based on GLIDE extra precision mode (**Table 4**).

The Hydrogen bonding, Glide Score, Glide Energy of the docked complex has been analyzed and the results were compared with the commercial drugs as an antiviral agent.

Docking studies showed that there is a ligand binding affinity of both the natural compounds and commercial drugs . Based on the XP docking results of neuraminidase with phytochemical compounds, oleanolic acid with glide score -5.4 and glide energy -40.03 kcal/mol and betulinic acid with glide score -5.2 and glide energy -39.7kcal/mol makes interaction with the active residue ARG371 at the active site pocket are chosen as potent compounds for treating influenza (**Figure 1**).

By analyzing the docked conformation of Hepatitis A Virus proteinase with the phytochemical compounds, magiferin with glide score -8.2 and glide energy -54.5 kcal/mol and curcumin with glide score -8.8 and glide energy -56.9kcal/mol makes interaction around the catalytic triad forming residues ASP84, HIS44, CYS172. The scaffold of these compounds may serve as best candidates for treating Hepatitis A disease (**Figure 2**).

Docking studies of herpes virus protease reveals bilobetin and amentoflavone are the potent candidates for treating Herpes virus infection based on their glide score -5.9, -5.4 and glide energy -35.4, -32.4 kcal/mol respectively. Similarly Rutin and hesperidin makes hydrogen bond with ARG155, HIS57 around the catalytic pocket of Hepatitis C Virus protease with least gilde score -7.9 and -7.8, and glide energy -54.9 and -52.2 kcal/mol respectively (**Figure 2**) .

Molecular docking studies of phytochemical compounds with the modeled Sindbis virus protease show ascorbic acid makes hydrogen bond interaction at S1 binding site ASN9 with glide score -7.2 and glide energy -42.6kcal/mol. The phytochemical compound juglone makes interaction at the S2 binding residue TRP89 with very least score -7.6 and glide energy -54.9kcal/mol. Hence these compounds may serve as useful scaffold for treating viral encephalitis (**Figure 3**).

Comparison of docked results of phytochemical compounds with the commercial drugs Zanamavir, Ribavirin, Acyclovir and Chloroquine for treating Influenza, Hepatitis, and viral meningitis and encephalitis, reveals natural compounds from plant sources are more potent than the commercial drugs based on glide score, glide energy and hydrogen bond interactions at the active site (**Figure 4**).

CONCLUSION: When the new inhibitors bind on the active site residue or the catalytic triad forming residues of Protease, the protease lacks the ability to cleave the poyprotein complex and so viral replication can be terminated. The nature hosts with more than 2000 species of plants whose phytochemical properties are still unveiled. Nature with infinite variety of flora is a gods gift of man. Clinical trials for all these might take ages to reveal their efficacy as a drug. Hence, *In silico* analysis of plants will help to identify the best lead compounds in a very short period and help in combating the dreadful disorders and diseases of this era.

ACKNOWLEDGEMENT: The authors thank Department of Biochemistry and Bioinformatics faculties or providing valuable support for the successful completion of this research work.

REFERENCES:

1. Peter C. McMinn. The molecular basis of virulence of the encephalitogenic flaviviruses. Journal of General Virology 1997, 78, 2711–2722.
2. Benjamin LA, Kelly M, Cohen D, Neuhann F, Galbraith S, Mallewa M, Hopkins M, Hart IJ, Guiver M, Lalloo DG,

Heyderman RS, Solomon T. Detection of herpes viruses in the cerebrospinal fluid of adults with suspected viral meningitis in Malawi. Infection. 2012 Jul 14.

3. Jomon KV, Sudharmini S Thomas T. Valamparampil. *Aedes* mosquitoes in arboviral epidemic prone area of kottayam district, kerala, India. short communication *academic review* 2009. *171-178*

4. Giovanni Maga, Sandra Gemma,Caterina Fattorusso, Giada A. Locatelli,Stefania Butini, Marco Persico, Gagan Kukreja, Maria Pia Romano, Luisa Chiasserini, Luisa Savini, Ettore Novellino, Vito Nacci, Silvio Spadari and Giuseppe Campiani. Specific Targeting of Hepatitis C Virus NS3 RNA Helicase. Discovery of the Potent and Selective Competitive Nucleotide-Mimicking Inhibitor QU663. Biochemistry 2005, 44 (28), 9637–9644
5. Shanta M. Zimmer, M.D., and Donald S. Burke (2009). Historical Perspective — Emergence of Influenza A (H1N1) Viruses. The New England Journal of Medicine, 361:279-85.
6. Grienke U, Schmidtke M, Kirchmair J, Pfarr K, Wutzler P, Dürrwald R, Wolber G, Liedl KR, Stuppner H, Rollinger JM. Antiviral Potential and Molecular Insight into Neuraminidase Inhibiting Diarylheptanoids from Alpinia katsumadai. Journal of Medicinal Chemistry 2010, 53, 778–786.
7. Ivanov *et al*. Base modified Ribonucleosides as potential Anti-Hepatitis C Virus agents. Nucleic acid symposium 2008. Series No. 48, 619-620.
8. Gupta Rachna Anna Wald, Elizabeth Krantz, Stacy Selke,Terri Warren, Mauricio Vargas-Cortes, Gerri Miller, and Lawrence Corey. Valacyclovir and Acyclovir for Suppression of Shedding of Herpes Simplex Virus in the Genital Tract. Journal of infectious diseases 2004. 190(8):1374-81
9. Gould E.A, B. Coutard. H. Malet , B. Morinb, S. Jamalb, S. Weaverc, A. Gorbalenyad, G. Moureaua, C. Barontia, I. Delogua, N. Forresterc, M. Khasnatinovg, T. Gritsunf, X. de Lamballeriea. Understanding the alphaviruses: Recent research on important emerging pathogens and progress towards their control. Antiviral Research 2010. 87(2):111-24
10. David and Frick. The Hepatitis C Virus NS3 Protein: A Model RNA Helicase and Potential Drug Target. Currrent. Issues Mol. Biol 2007. 9: 1–20
11. Polgár L**.** The catalytic triad of serine peptidases**.** Cellular and Molecular Life Sciences 2005. (62) 2161–2172.
12. Russo, A.T.,White, M.A.,Watowich, S.J. The crystal structure of the Venezuelan equine encephalitis alphavirus nsP2 protease. Structure 2006. 14, 1449–1458.
13. Gorbalenya, A. E. Two related superfamilies of putative helicases involved in replication, recombination, repair and expression of DNA and RNA genomes. Nucleic Acids Research 1989. *17*, 4713-4729
14. Chien-Shu Chen *et al.* Structure-Based Discovery of Triphenylmethane Derivatives as Inhibitors of Hepatitis C Virus Helicase. Journal of. Medicinal. Chemistry 2009. *52,* 2716–2723.

How to cite this article:
Ramaiah R and Suresh PC: Molecular Docking Studies of Phytochemical Compounds with Viral Proteases. *Int J Pharm Sci Res*. 2013; 4(1); 475-482.