Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 4, Suppl 1, 2012

Research Article

EVALUATION OF ANTI-INFLUENZA ACTIVITY OF CURCUMIN DERIVATIVES BY DOCKING AND PHARMACOPHORE MODELING APPROACH

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Received: 28 Oct 2011, Revised and Accepted: 17 Dec 2011

ABSTRACT

Curcuma longa plant produces Curcumin which is widely used as spices and colouring agent in food. Curcumin is also used to treat various diseases due to its medicinal and pharmacological activities. The present study is based on analysis of anti-influenza activity of Curcumin by using computational methods. The Curcumin derivatives obtained from the data base were docked against the HA protein of influenza (2009 H1N1) virus. Further analysis by evaluating the biological activity and pharmacophore modeling results about the pharmacophoric features responsible for the inhibition activity. The results demonstrated that some of the specific Curcumin derivatives can be successfully used against influenza virus infection.

Keywords: Curcumin, Docking, Pharmacophore modeling, Hemaglutinin

INTRODUCTION

Nature has provided the important sources of remedies to cure almost all diseases in human and these medicines are produced from natural source, especially from plants[1].Curcumin as a major chemical component of turmeric plant (*Curcuma longa*), has been used as a major component of Indian Ayurvedic medicine to treat various health problems[2]. Recent research has also identified the Curcumin as a potential molecule for many of the biological activity of turmeric. The chemical constituent of Curcumin molecules are polyphenols and are responsible for the yellow colour of turmeric and can exist in their tautomeric forms, keto and enol[3].Curcumin molecules also incorporates several functional groups and the aromatic ring systems the carbonyl groups form a diketone[4].Recently the clinical trials in humans are going on to investigate the effect of Curcumin on various diseases including multiple myeloma, pancreatic cancer, myelodysplastic syndromes, colon cancer, arthritis, and Alzheimer's disease etc[5,6,7,8]. Based on the function various synthetic derivatives are also has been designed for Curcumin to treat cancer[9]. Influenza A virus strain 2009 H1N1 is a highly pathogenic strain hence worldwide attention is due to the outbreaks in sporadic human infections with a high fatality rate[10]. The influenza virus genome consists of eight negative stranded RNA segments encoding 11 viral proteins; among those, the major glycoproteins on the viral surface, haemagglutinin (HA) and neuraminidase (NA), are two of the main target antigens of the host immune system[11]. Due to the pre-existing antiviral resistance to the drug amantadine and the emergence of H1N1 variants resistant to Oseltamivir and Zanamivir, demands the need for developing new antiviral therapeutic molecules[12].Devlopment of new drug molecule includes many computational study. For example after selection of a target protein the analysis for an effective drug molecule requires methods like molecular docking which evaluates the bioactivity of a molecule[13]. Along with docking the pharmacophore modelling methods are also exhibits good to evaluate the inhibition activity against the specific target[14].

So the computational methods can also be effectively used to find out the Curcumin derivatives as the potential drug molecules against swine flu. The objective of the present work is to evaluate of anti-influenza activity of Curcumin derivatives by insilico based method. The methods include molecular docking of the Curcumin derivatives with Hemaglutinin protein followed by extensive analysis of the binding site. Further by pharmacophore modelling is used to figure out the pharmacophoric feature of selected Cucumin molecules.

MATERIALS AND METHODS

Retrieval of Ligands and target information

The structural information of Curcumin derivatives were retrieved from Pubchem data base available in NCBI server (http://pubchem.ncbi.nlm.nih.gov/). The SMILE formats of the molecular structure obtained from Pubchem were converted to the protein data bank format by using Marvin Sketch 5.0 tool (http://www.chemaxon.com/marvin/sketch/index.jsp). The energy minimization of the retrieved structures were done by using PRODRG server which is available at http://davapc1.bioch.dundee.ac.uk/prodrg/.PRODRG is a useful server which takes the 3D co-ordinate of small molecules and generates a variety of topology file of the ligand widely useful for further docking and molecular dynamics simulation. The target protein for HA were retrieved from Protein Data bank (PDB).The Protein Data Bank is a universal repository for the 3-D structural data of large biological molecules, such as proteins and nucleic acids. The data are basically obtained by X-ray crystallography or NMR spectroscopy and submitted by biologists and biochemists are freely on the Internet for use[15].

Docking study by Autodock

Docking study was performed with the Curcumin ligands and HA protein by using Autodock software which is in the version 4.2.[16] AutoDock is a suite of automated docking tools. It is designed to predict how small molecules, such as substrates or drug candidates, bind to a receptor of known 3D structure. Lamarckian Genetic Algorithm was chosen for docking and which was run for 50 generation. Docking is a very reliable method for preliminary selection of ligand activity with its receptors. So based on binding energy the suitable complexes can be selected and analysed.

Pharmacophore modeling study

Pharmacophore modelling analysis study is basically performed to figure out the bioactive part of a ligand molecule, after binding with a suitable receptor. The pharmacophore analysis study was carried out using the software Ligand Scout (version 2.02). Ligand Scout is a software tool that allows to derive the 3D chemical feature-based pharma-cophores from structural data of macromolecule and ligand complexes in a fully automated and convenient way[17].Various pharmacophoric features were obtained and superimposition was done to observe the common pharmacophore of the ligand molecules.

RESULTS AND DISCUSSION

To study the anti- influenza activity of Curcumin derivatives, HA protein was considered the receptor for the present study and was obtained from protein data bank (PDB ID 3AL4) [18].Pre-processing of this protein was performed by removing the metal ions and crystal waters and hydrogen atoms are added. Similarly all total 22 numbers of Curcumin derivatives were selected. The docking was performed and binding energy (BE) was obtained has been

presented in Table 1. After docking among all the derivatives based on good binding energy, the ligands were considered. The condition that was chosen to select the best ligands is after docking those ligands showed binding energy value less than equal to - 8.0. Only four numbers of best scored complexes were considered which are Curcumin derivatives serial number 3,8,18 and 19 that are highlighted as bold in Table 1. These four complexes were further analysed to observe the shared pharmacophore in their structure by aligning the ligands using Ligand scout tool. The alignment of the ligands from the complexes with HA protein provides the common most shared features of the ligands and it is shown by round circles are given in Fig.1.Further study from the docked complex to obtain the desired pharmacophore of ligand molecules has been performed by pharmacophore modeling method. The method is more useful to select out the active part of a set of drug molecules having potential to cure the disease[19].The inhibition study of Curcumin molecules and Hemaglutinin protein of H1N1 virus has studied earlier and it has shown its effectiveness[20]**.** The docking results of Curcumin were observed as it is having good binding affinity towards Hemaglutinin protein. Then using the Ligand scout tool for all the docked complexes molecules resulted the major pharmacophoric features like hydrogen bond donor (HBD), hydrogen bond acceptor (HBA), aromatic ring (AR), hydrophobic interaction (HI) and minor features as Positive ionic surface area (PIA), negative polar surface area (NIA) as given in Table 1. The pharamcophoric features computed for the selected Curcumin derivatives were observed to be consistent for some features.

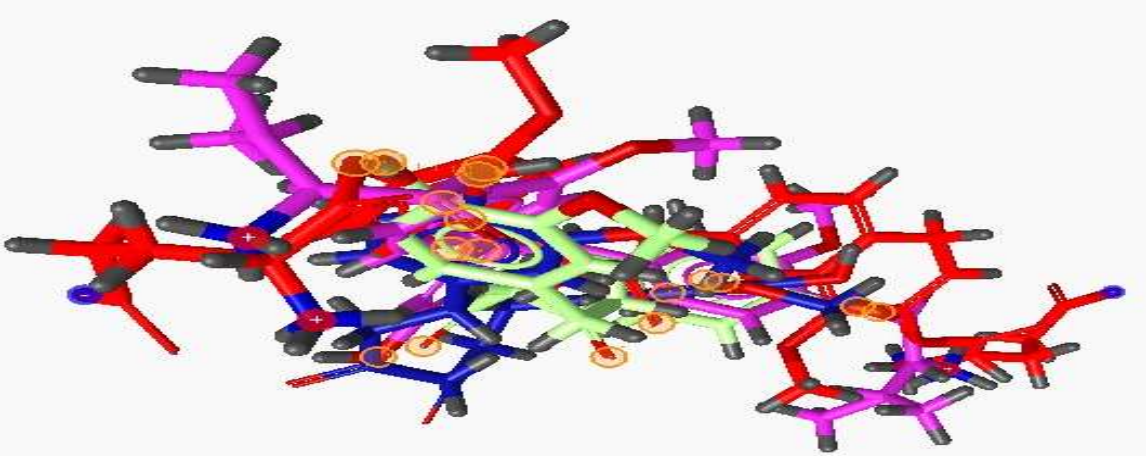
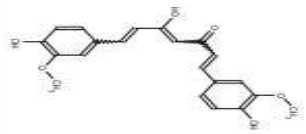
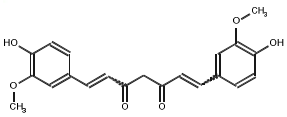
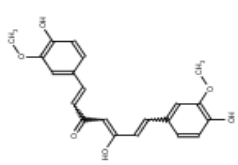
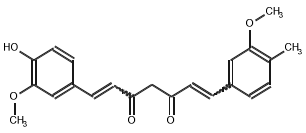
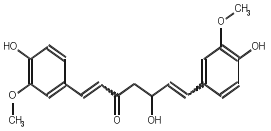
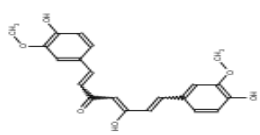
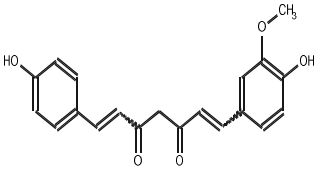
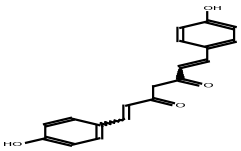
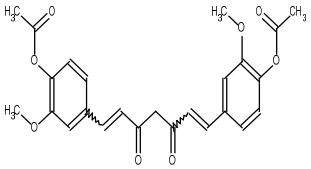
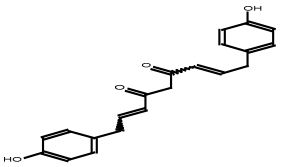
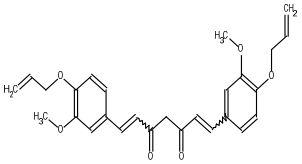
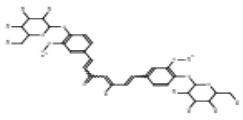
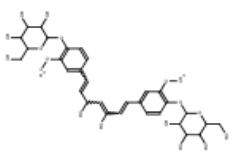
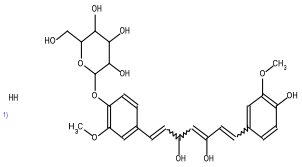
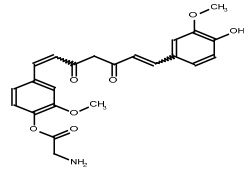
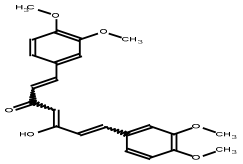
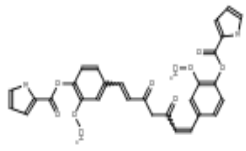
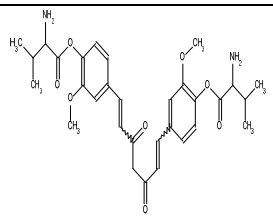
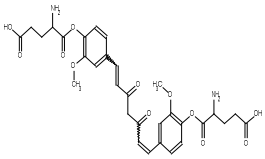
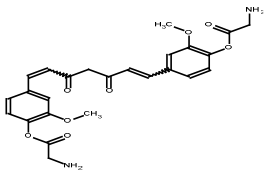
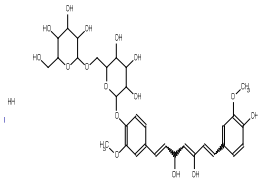
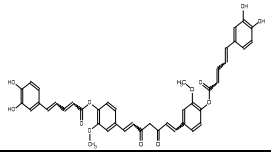


Fig. 1: Showing the aligned feature of pharmacophoric features of selected 4 Curcumin derivatives

Table 1: Selected Curcumin derivatives, pharamcophoric features and their binding energy and residues with HA protein

Sl. No	Structures	HBD	HBA	PIA	NIA	HI	AR	BE	Binding Residues
1		+2	+6	-	-	+2	+2	-7.47	SER77 ALA79 LYS289
2		+2	+6	-	-	+2	+2	-6.63	PHE117 ALA79 THR78 HIS57 LEU56
3		+2	+6	-	-	+2	+2	-8.29	CYS73 TRP66 THR78 PHE261 SER274 THR276 ASP275 LYS289
4		+2	+6	-	-	+2	+2	-6.45	LYS289 SER80 ALA54 LYS42 LEU76
5		+1	+5	-	-	+2	+2	-7.69	ASP275 ARG119 PHE117 THR78 SER75
6		+2	+6	-	-	+2	+2	-7.23	TRP66 ASN153 PHE261 THR78 ASP275

7		+2	+6	-	-	+2	+2	-7.29	LYS289 ASP275 SER274 THR276
8		+2	+5	-	-	+2	+2	-8.5	ASN153 TRP66 PHE261 THR78 PRO288 HIS302 LYS289
9		+2	+4	-	-	+2	+2	-7.7	ILE304 LEU89 CYS309 GLN62 THR64 THR61 THR305
10		-	+8	-	-	+2	+2	-5.6	LYS 314 PHE63 ARG51
11		+2	+4	-	-	+2	+2	-6.95	LYS68 ALA65 GLY268 ILE172 VAL53 THR64
12		-	+6	-	-	+4	+2	-6.07	ARG51 ALA267 LYS82 PHE63
13		+5	+11	-	-	+2	+2	-7.6	LYS314 SER80 ASN300 ARG51 SER113 PHE63 THR61 LYS308
14		+3	+8	-	-	+2	+2	-7.23	PHE120 ILE172 TYR171 TYR259 ASP275 SER274
15		+2	+6	+1	-	+3	+1	-6.95	ALA267 SER115 ILE172 VAL53 PHE63 GLN62
16		-	+4	-	-	+2	+2	-7.36	THR78 ASP275 ARG119 LYS175
17		-	+8	-	-	+4	+4	-7.0	LEU76C HIS57 LYS9C ALA54

18		+3	+7	+2		+5	-	-8.36	PRO288 SER274 ASP275 ILE271 ILE273 TYR104 GLU105
19		+2	+11	+2	+2	+2	+1	-8.28	GLU118 LYS177 LYS314 ASN60 THR284 LYS308 MET59 LYS289
20		+2	+7	+2	-	+2	+2	-6.92	GLU78 PHE70 ASP275 ILE273
21		+6	+12	-	-	+2	+2	-6.29	LYS308 ARG51 PHE63 LYS82 GLU121 ARG119 LYS177
22		+5	+11	-	-	+5	+4	-7.07	GLU40 ALA79 ALA54 LEU76 THR78

It was observed that all the groups of the molecule shares same orientation in the complex irrespective of their binding residues except few residues common in case of derivative 3 and 9.Two common pharmacophoric features as hydrophobic interaction and hydrogen bond acceptor were found to be suitably shared among four selected derivatives. The distance between the shared features is computed as 0.559 nanometre as shown in Figure 2. Previously the quantitative structural activity relationship has been performed with the fact that the physiochemical parameters are mainly responsible for binding affinity of the Curcumin derivatives[21].QSAR analysis is an effective way to find out the appropriate combination of descriptors that lead to predict the bioactivity of the compounds. As the hydrogen, hydrophobic and ionic interactions are considered to be the major driven forces for ligand binding to receptor, our result obtained in this docking and pharmacophore analysis is also in a good agreement with this fact.

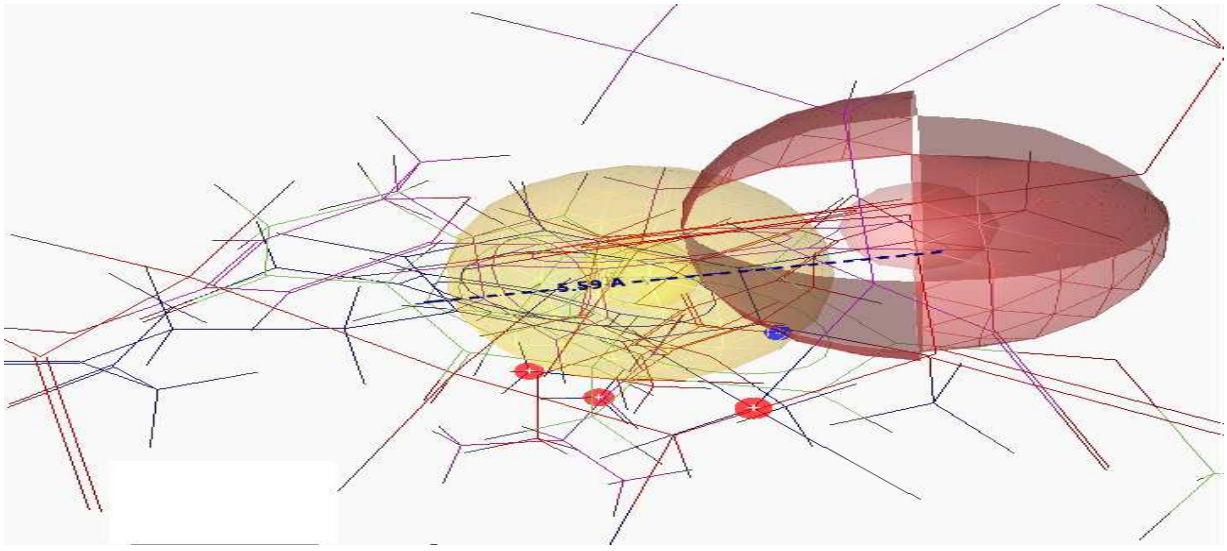


Fig. 2: Predicted pharmacophores as hydrophobic interactions (Yellow colour) and Hydrogen bond donors (Red colour) of selected Curcumin derivatives

Due to the worldwide spread of H1N1 avian influenza with high virulence has recently provides a potential threat to human as being pandemic in nature[22]. In addition to the viral, neuraminidase (NA) the HA protein has been found to be a potential target to control influenza virus. By using computational methods with an understanding of the ligand binding mechanism between 3D structures of HA protein and Curcumin inhibitors provides a useful method to select out the potential Curcumin derivatives.

CONCLUSION

From our in-silico based docking study it can be concluded that, some particular Curcumin derivatives are potential inhibitors of HA protein. Also from the analysis, the pharmacophoric features of the selected Curcumin derivatives were predicted as hydrophobic interaction and hydrogen bond acceptor. Hence along with docking study, ligand based molecular modelling methods are very much useful to screen and predict particular bioactive compounds from a group of related compounds.

ACKNOWLEDGMENT

We are thankful to Chief executive, Majhighariani Institute of Technology & Science, (MITS) Rayagada for his encouragement and providing computing facility at MIRC lab.

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