INTERNATIONAL JOURNAL OF APPLIED BIOLOGY AND PHARMACEUTICAL TECHNOLOGY

www.ijabpt.com Volume-5, Issue-1, Jan-Mar-2014 Coden : IJABPT Copyrights@2014

ISSN : 0976-4550

Received: 1st Dec-2013 *Revised: 6th Dec-2013* *Accepted: 7th Dec-2013*

Research article

MOLECULAR DOCKING ANALYSIS OF FEW COMPOUNDS FROM *CURCUMA LONGA* AND *HEDYCHIUM CORONARIUM*

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ABSTRACT : Molecular Docking is safe and easy to use tool helps in investigating, interpreting, explaining and identification of molecular properties using three-dimensional structures. Molecular docking is used to predict the structure of the intermolecular complex formed between two or more molecules. When a structure is available for the target, computer-based screening using molecular docking was considered. In the present study, all nine ligands tested against peptide deformylase, New Delhi Metallo-beta-Lactamase-1 and dehydrosqualene synthase resulted in curcumin I as the best compound which showed greater binding affinity towards the active site amino acids of each protein. *Curcuma longa* and *Hedychium coronarium* were carried out to test their effective rate of inhibitions against selective protein targets from *E. coli, K. pneumonia* and *S. aureus* respectively.

Key Words: Molecular docking, *Curcuma longa, Hedychium coronarium,* ligands, amino acids.

INTRODUCTION

Curcuma longa and *Hedychium coronarium* belongs to the family Zingiberaceae comprising of about 80 rhizomatous species. Curcumin has also long been part of the daily diet in Asian countries and has not been shown to cause any toxicity. (Ammon and Wahl, 1991), Extensive research over the past 30 years has indicated that this molecule has therapeutic potential against a wide range of diseases, such as cancer, lung diseases, neurological diseases, liver diseases, metabolic diseases, autoimmune diseases, cardiovascular diseases, and various other inflammatory diseases.(Clauuen, 2001, jayasimha et al, 2013). How a single agent can possess these diverse effects has been an enigma over the years. However, numerous lines of evidence indicate that curcumin is highly pleiotropic with anti-inflammatory, (Jones, 1997, Goodsell and Olson, 1996, Goel ajay and Agarwal, 2010) hypoglycemic, (Hatcher et al, 2008, Pubchem) antioxidant (Ishita et al, 2004) wound healing, (Jones et al, 1997) and anti-microbial activities.(Kapoor, 2009) It has been shown to possess chemo sensitization, chemotherapeutic, and radio sensitization activities as well (Lavalle, 2000 and Lu Sy, 2010). Many clinical trials using curcumin as a therapeutic agent are under way.[14] *Hedychium coronarium* is a perennial herb, the rhizome is used for the treatment of tonsillitis, infected nostrils, tumor and fever also used as a febrifuge, tonic, excitant and anti- rheumatic antirheumatic, excitant, febrifuge and tonic. Molecular docking is used to predict the structure of the intermolecular complex formed between two or more molecules (Morris, 2009). The most interesting case is the protein-ligand interaction, because of its applications in medicine. Ligand is a small molecule, which interacts with protein's binding sites. Binding sites are areas of protein known to be active in forming of compounds (Momany, 1992). In this study, molecular docking analysis of few compounds from *Curcuma longa* and *Hedychium coronarium* were carried out to test their effective rate of inhibitions against selective protein targets from *E. coli, K. pneumonia* and *S. aureus* respectively. Bacterial peptide deformylase (PDF) belongs to a sub-family of metalloproteases that catalyse the removal of the N-terminal formyl group from newly synthesized proteins. PDF is essential in prokaryotes and conserved throughout the eubacteria. It is therefore considered an attractive target for developing new antibacterial agents. Staphylococcus aureus produces hospital- and community-acquired infections, with methicillin-resistant S. aureus posing a serious public health threat. The golden carotenoid pigment of S. aureus, staphyloxanthin, promotes resistance to reactive oxygen species and host neutrophil-based killing, and early enzymatic steps in staphyloxanthin production resemble those for cholesterol biosynthesis. (Rarey, 1996).

MATERIALS AND METHODS

Crystal structures of proteins selected for the study

The crystal structures of *E. coli* peptide deformylase (PDB ID: 1LRU), *K. pneumonia* New Delhi Metallo-beta-Lactamase-1 (PDB ID: 4HL1) and *S. aureus* dehydrosqualene synthase (PDB ID: 2ZCQ) were extracted from Protein Data Bank [www.rcsb.org/pdb] and these target structures are used for molecular docking study using Molegro Virtual Docker. Before docking all these protein crystal structures were cleaned by removing the heteroatoms such as ligands, ions, water molecules etc. H-atoms were added to correct ionization and tautomeric states of amino acid residues.(Rong chen, 2003).

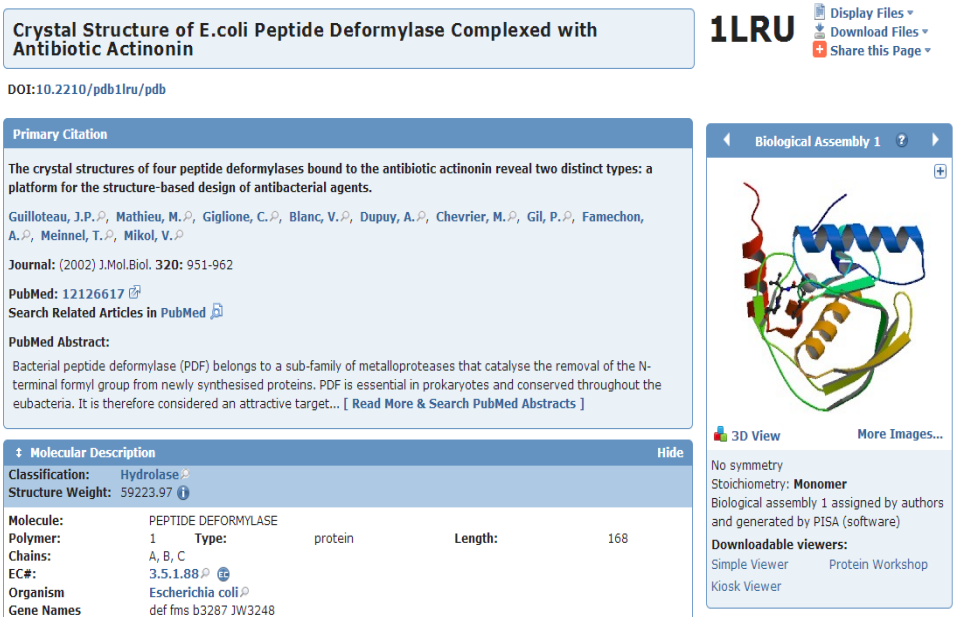

Figure 1. PDB entry for 1LRU

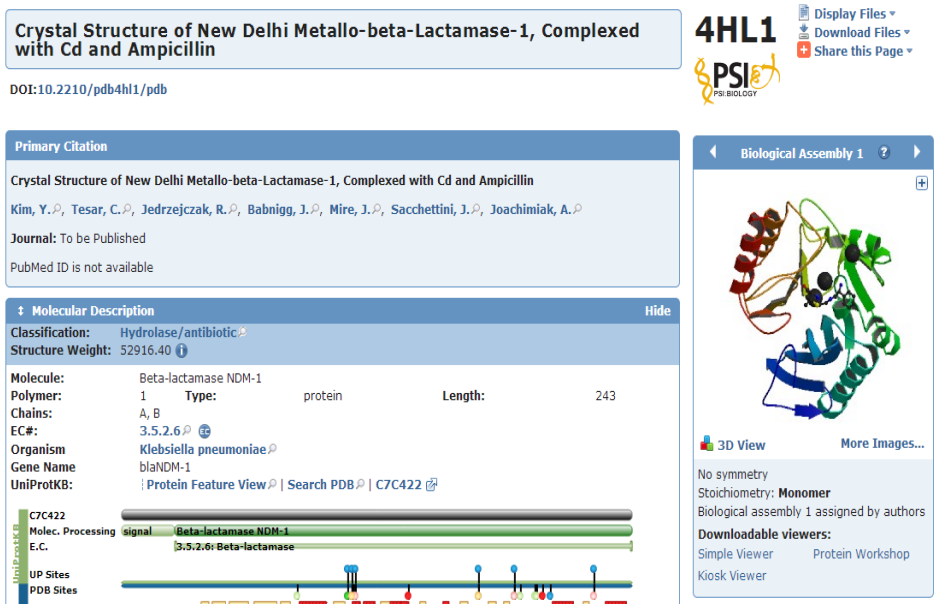

Figure 2. PDB entry for 4HL1

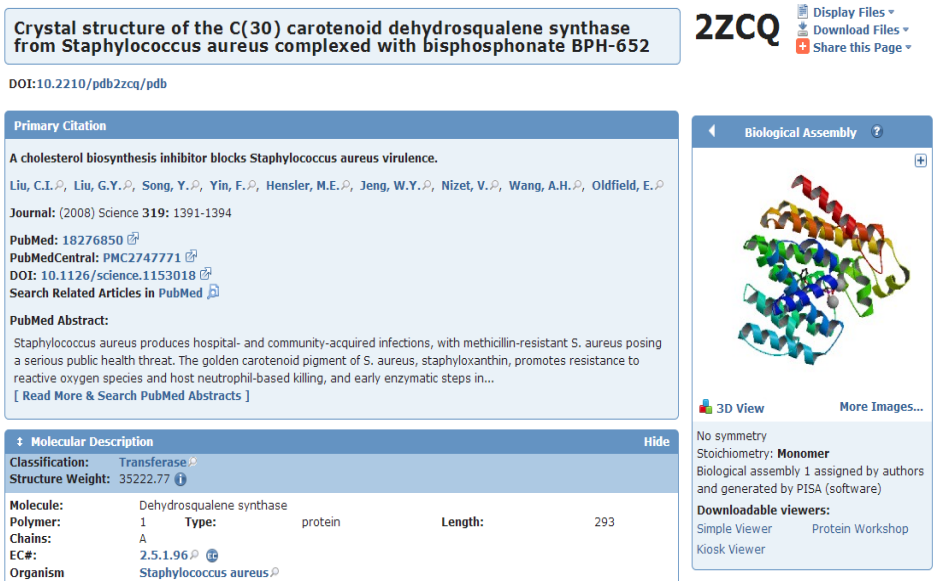

Figure 3. PDB entry for 2ZCQ

Molegro Virtual Docker

Molegro Virtual Docker (MVD) is advanced docking analysis software used to predict protein-ligand interactions. The potential binding site of the target protein and lead candidates are identified by a molecular docking algorithm called Mol Dock, which is based on a novel search algorithm that combines differential evolution technique with a cavity prediction algorithm. Genetic algorithm, Mol Dock SE with default parameters such as 1500 iterations, population size 50, with maximum 300 steps is used. The scoring scheme was derived from PLP [Piecewise Linear Potential] scoring functions [http://www.molegro.com/index.php]

Ligand molecules selected for docking

A total of 9 ligand structures are extracted from literature and the images are given below. Coronarin I, II and III are selected from *Hedychium coronarium* and curcumin I, II, III and Ar-tumerone, tumerone and curlone are selected from *Curcuma longa.*

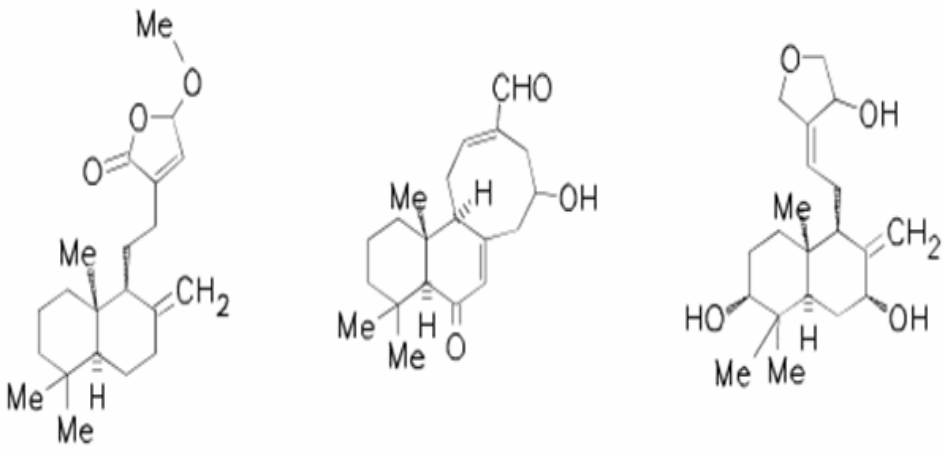

Figure 4. Structures of coronarin I, II and III from *Hedychium coronarium*

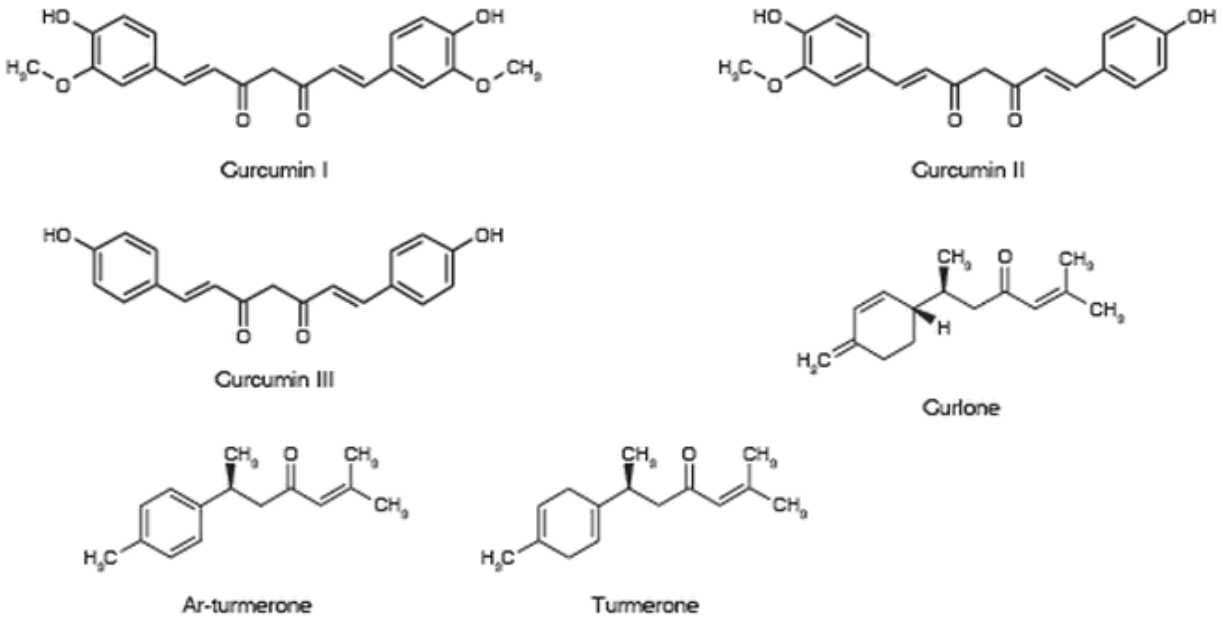

Figure 4. Structures of curcumin I, II, III and Ar-tumerone, tumerone and curlone from *Curcuma longa*

RESULTS AND DISCUSSION

Docking runs of all known co-crystallized bound ligands to 1LRU, 4HL and 2ZCQ as well as 9 ligands from literature was carried out using Molegro Virtual Docker. The final docking score was calculated in terms of kcal/mol for each docking experiment. The analysis of docking score and Hydrogen bond interactions was done for all ligand molecules. The ligands with their binding energies and hydrogen bond interactions with active site amino acid residues of target proteins are given in Tables 1-3. Prior to docking, all ligands are evaluated for physico-chemical properties and found to be within the limits of Lipinski's rule of 5 (Table 1).

Table 1. Ligands exhibiting physico-chemical properties within Lipinski rule of 5 range.

	Molecular Weight	H-Bond Acceptors	H-Bond Donors	LogP	Rotatable Bonds
Coronarin 1.mol	332.53	3	0	4.97	4
Coronarin 2.mol	302.45	3	1	2.4054	1
Coronarin 3.mol	336.52	4	3	2.2145	3
Ar-turmerone.mol	216.35	1	0	3.7387	5
curcumin1.mol	368.41	6	2	2.4793	10
curcumin2.mol	338.38	5	2	2.732	9
curcumin3.mol	308.35	4	2	2.9847	8
curlone.mol	218.37	1	0	3.1441	5
tumerone.mol	218.37	1	0	2.9219	5

Molecular interactions between *Curcuma longa* and *Hedychium coronarium* ligands versus 1RLU, peptide deformylase was given in Table 2. The given conformation state of this enzyme deposited in PDB was taken in the molecular docking analysis with the set of compounds. It was found that Actinonin, which is 1LRU bound ligand made 7 H-bond interactions with active site amino acids with -144.869 kcal/mol binding energy. It should be noted that 9 ligands under study scored docking energies between -92.242 to -134.867 kcal/mol only. Majority of ligands displayed H-bond interactions with Arg97.

Table 2. Binding energies and hydrogen bond interactions of ligands with active site amino acid residues of 1LRU

Ligand	Binding Energy (kcal/mol)	No. of H-bond interactions	Interacting residues
1LRU bound ligand	-144.869	7	Gly43, Gly45, Gln50, Gly89(2), Leu91, Glu133,
Coronarin 1.mol	-123.167	4	Gln50, Leu91, Ile44, Gly45
Coronarin 2.mol	-99.106	2	Arg97(2)
Coronarin 3.mol	-110.099	5	Glu41, Glu42, Ile44, Gly45
Ar-turmerone.mol	-95.512	1	Ile44
curcumin1.mol	-134.867	3	Glu87, Arg97(2)
curcumin2.mol	-130.229	4	Gly45(2), Arg97, Glu133,
curcumin3.mol	-122.056	3	Cys129, Glu42, Arg97
curlone.mol	-93.426	1	Cys129
tumerone.mol	-92.242	1	Cys129

Table 3 reported the energy contributions between tested ligands and 4HL1 protein from *K. pneumonia*. 4HL1 which is complexed with antibiotic Ampicillin resulted in dock score / binding energy of -99.142 kcal/mol making 5 H-bond interactions with active site amino acids of New Delhi Metallo-beta-Lactamase-1. Of all the tested ligands, Curcumin I reported to exhibit favorable interactions and geometry with active site region of 4HL1 making 6 H-bond interactions with a binding energy of -138.743 kcal/mol (Figure 5). The dock scores were in the range -86.210 to -138.743 kcal/mol respectively.

Table 3. Binding energies and hydrogen bond interactions of ligands with active site amino acid residues of 4HL1

Ligand	Binding Energy (kcal/mol)	No. of H-bond interactions	Interacting residues
4HL1 bound ligand	-99.142	5	Asp124, Lys211(2), His189, Asn220
Coronarin 1.mol	-117.042	2	Asp212, Ser251
Coronarin 2.mol	-90.250	6	Lys211, His120, His189, Gln123, Asp124
Coronarin 3.mol	-100.552	8	Lys216, Ser217, Ile210, Ser251, Asp212
Ar-turmerone.mol	-87.367	0	-
curcumin1.mol	-138.743	6	Gln123, Lys211, Asp212, Ser251
curcumin2.mol	-130.488	5	Gln123, Cys208, Asp212, Ser251
curcumin3.mol	-135.389	6	Gln123, Asp124, Lys211, Asn220, His189, Asp223
curlone.mol	-87.635	1	Asp212
tumerone.mol	-86.210	2	Asp212, Ser251

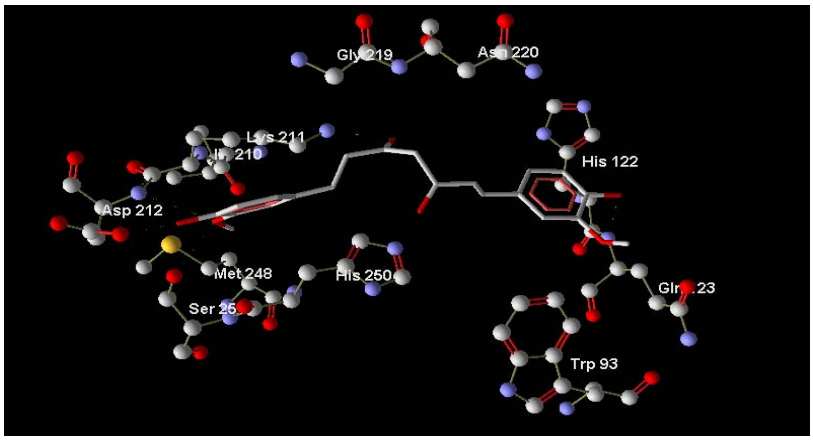

Figure 5. Docked orientation of curcumin I showing H-bond interactions with active site amino acids of 4HL1

Molecular docking analysis of 2ZCQ, *S. aureus* dehydrosqualene synthase complexed with Bisphosphonate resulted in dock score of -139.799 kcal/mol with 11 H-bond interactions, whereas set of 9 ligands displayed binding energy range from -91.693 to -158.387 kcal/mol respectively. Though Curcumin I has two H-bond interactions with active site amino acids of 2ZCQ, the binding energy was found to be -158.387 kcal/mol (Figure 6), such energy is expected to be due to favorable hydrophobic interactions between ligand atoms and receptor amino acids.

Table 4. Binding energies and hydrogen bond interactions of ligands with active site amino acid residues of 2ZCQ

Ligand	Binding Energy (kcal/mol)	No. of H-bond interactions	Interacting residues
2ZCQ bound ligand	-139.799	11	Ser19, Ser21, Arg45, Arg171, Arg265, Asn168, Tyr248
Coronarin 1.mol	-125.76	1	Cys44
Coronarin 2.mol	-97.012	0	-
Coronarin 3.mol	-107.544	2	Val133, Gln165
Ar-turmerone.mol	-92.802	0	-
curcumin1.mol	-158.387	2	Arg45, Gly161
curcumin2.mol	-151.451	2	Arg45, Gly161
curcumin3.mol	-131.927	1	Val37
curlone.mol	-92.749	0	-
tumerone.mol	-91.693	1	Tyr248

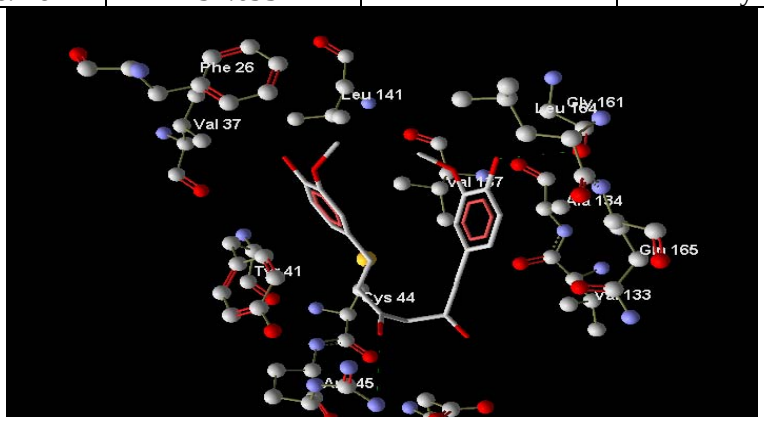

Figure 6. Docked orientation of curcumin I showing H-bond interactions with active site amino acids of 2ZCQ

CONCLUSION

The molecular docking analysis presented in this paper suggested that of all 9 ligands tested against peptide deformylase, New Delhi Metallo-beta-Lactamase-1 and dehydrosqualene synthase resulted in curcumin I as the best compound which showed greater binding affinity towards the active site amino acids of each protein. Moreover, the contributing amino acids in interaction possess the same set of common physico-chemical properties that imparts stability to the interaction. Further, work needs to be extended to study on all possible druggable targets in pathogenic bacteria.

ACKNOWLEDGEMENT

The authors express gratitude to Dr.S.Harasreeramulu Head of the Department of Biotechnology for providing research facilities for carrying out the experimental work and for his kind support.

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