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ORIGINAL ARTICLE

In Silico Identification of Protein and Protein Docking Using Cheminformatics With Anticancer Property in Penaeus Sp

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ABSTRACT
Fragment-based drug discovery approaches have recently gained prominence as a distinct and complementary to drug discovery. Anticancer proteins present in the species such as Fennero penaeus indicus, Penaeus monodon, Litopenaeus vannamei and Metapenaeusensis were determined based on binding affinities against the cancer proteins causing human Lung, Blood, Pancreatic, Breast and Colon Cancer were identified and validated with protein-protein docking servers. The molecular conserved regions of the retrieved protein sequences are identified using T-COFFEE server and applied into CPH model server to predict the three dimensional structure of the target proteins. These studies were performed using advanced automated Protein – protein docking server called CLUSPRO. On comparing the docking values, the protein C Type Lectin of Fennero penaeus indicus shows higher binding affinity value is (-1282.5) and followed by Penaeus monodon (-1169.5) and Metapenaeus ensis (-1101.3) for lung cancer gene (CHRNA3). For the blood cancer gene (MLLT10), Metapenaeus ensis protein shows higher binding affinity value (-1010.3). Penaeus monodon binding affinity (-1013.4) with colon cancer (DCC), Based on the affinities we conclude that the proteins (CHRNA3) are best candidate Inhibitors (drug) for human cancers.
Keywords: Protein-protein docking, Penaeus sp, Anticancer

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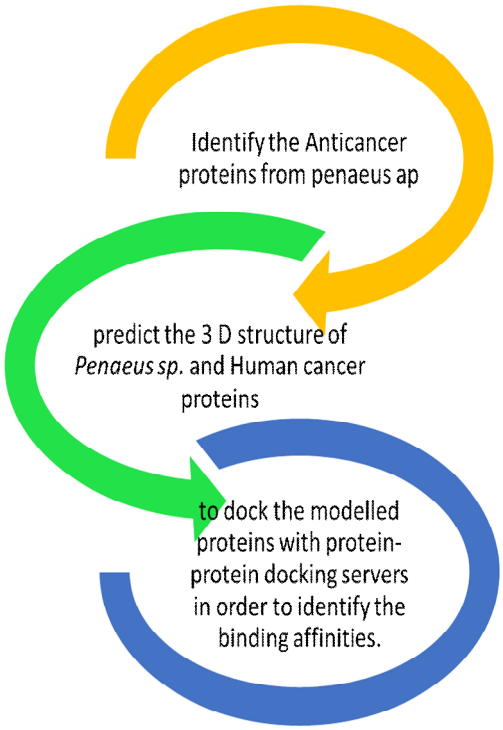
INTRODUCTION

Cancer remains one of the most life threatening diseases in worldwide. As per the World Health Organization report [1], in the year of 2018 approximately 18.1 million new cases of cancer reported globally and 9.6 million cancer deaths in 2018. In both sexes combined, lung cancer is the most commonly diagnosed cancer (11.6% of the total cases) and the leading cause of cancer death (18.4% of the total cancer deaths), closely followed by female breast cancer (11.6%), prostate cancer (7.1%), and colorectal cancer (6.1%) for incidence and stomach cancer (9.2%), and liver cancer (8.2%) for mortality. Lung cancer is the most frequent and the leading cause of cancer death among males, followed by prostate and colorectal cancer (for incidence) liver and stomach cancer (for mortality). Among females, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death, followed by colorectal and lung cancer (for incidence), and vice versa (for mortality); cervical cancer ranks fourth for both incidence and mortality. The most frequently diagnosed cancer and the leading cause of cancer death [2].

In the recent years, more emphasis has been placed on identifying marine-derived compounds that can be used as an effective treatment for life-threatening diseases such as cancer. Valentin A. Stonik *et al*., [4] have been reported that many marine-derived polysaccharides from Brown algae, Red algae, Green algae, marine bacteria, marine fungi, and marine animals such as sea cucumber, ascidian etc., and their analogues showing anticancer and cancer preventive properties. Celso Alves *et al*., [5] review focused on the bioactive molecules from algae with antitumor potential and concluded that algae *Sphaerococcus coronopifolius* as a producer of cytotoxic compounds. Suyeon Kim, [3] published a review article about the antimicrobial, antioxidant, anti-inflammtory and anticaner acivities of chitosan and its derivatives based upon the Deacetylation degree (DDA) and molecular weight (MW).

Anticancer peptide fractions from shrimp waste proteins has the potential for novel nutraceutical ingredient applications, Peptide fractions (<10 and 10-30 kDa) obtained from shrimp shell whites (Gulf of Mexico) as well as from langostino shells (El Salvador) significantly inhibited the growth of both colon and liver cancer cells by 60%, while < 10 kDa fraction from shrimp shells (FL) inhibited growth of liver cancer cells alone by 55% [6]. The number of proteins with a known three-dimensional structure is increasing rapidly, and structures produced by structural genomics initiatives are beginning to become publicly available [7, 8]. Kumaran, M. S *et al*., [21] investigated the MAGE inhibitors in the treatment of lung cancer by interactions between the target compounds and the amino acid residues of the MAGE (melanoma antigen) protein with the phytochemicals of *Naringi crenulata* by molecular docking method. Their results have shown binding pose between from - 6.54 to -15.34.out of five compound 1,2-benzenedicarboxylic acid show best ligand energy -8.15Kcal/mol with 3 hydrogen bond of distance is 2.1,3.0 and 2.3 Alexander Goncearenco *et al*., [4] explored the computational protocol to aid the design of small molecule and peptide drugs that target protein-protein interactions, particularly for anti-cancer therapy. With the structure of a target and its active or binding site, high-throughout docking is used as a hit identification tool. We have employed binding affinities of proteins with best anticancer activity properties in the screening of the same four shrimps in the validation studies by protein-protein docking. Venkata reddy Gayam *et al.,* [23], followed the molecular docking studies for novel series of quinoline-based hybrid molecules were designed and synthesized for anticancer. The synthesized molecules showed significant in vitro anticancer activity especially against CML (Chronic myeloenous leukemia) Cells (K562). M.C Kamaraj *et al.,* [26] investigated the inhibitory activity of the compounds of methanolic bark extract of *Shorea robusta* on hepatocellular carcinoma by molecular docking studies and to analyze the ADMET properties of the isolated compounds namely alpha amyrin and Beta amyrin. These compounds are used for docking on human oncogene protein 121p. The ΔG° recorded for alpha and beta amyrin binding with human Ras protein was -9.36 kcal/mol and -8.90 kcal/mol respectively.
The principal objectives of the present bioinformatics work are as follows:



MATERIAL AND METHODS

Literature Collection

The protein sequence information of C-type lectin in *Penaeusmonodon*, *Fenneropenaeusindicus*, *Litopenaeusvannamei*, *Metapenaeusensis* and Human cancers gene studies were done using Pubmed, PMC and OMIM database. http://www.ncbi.nlm.nih.gov/PMC/ . http://www.ncbi.nlm.nih.gov/pubmed/.

SRS: Sequence Retrieval system

The C-type lectin protein sequences were retrieved from NCBI protein databases in FASTA format in order to predict the protein modeling and docking studies. http://www.ncbi.nlm.nih.gov/

Multiple Sequence alignment:
The molecular conserved regions of the retrieved protein sequences are identified using T-COFFEE server. www.tcoffee.org/

Protein modeling:
The identified protein sequences are applied into CPH model server to predict the three dimensional structure of the target proteins. http://www.cbs.dtu.dk/services/CPHmodels/.

Protein-Protein Docking:
The protein –protein docking studies were performed using advanced automated Protein – protein docking server called CLUSPRO. nrc.bu.edu/cluster/.

Molecular visualization tools:
The three dimensional protein structures and the docked protein complexes are viewed with help of advanced molecular visualizations tool like Discovery studio software, Molegro molecular Viewer and Molsoft software are used to identify the binding regions of the protein complexes. http://accelrys.com/products/discovery-studio/.www.molegro.com/mmv-product.php. www.molsoft.com/.

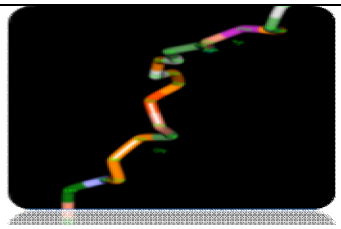
RESULTS

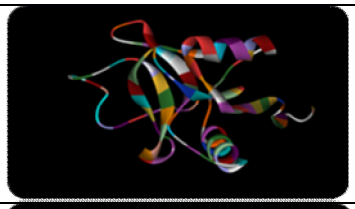
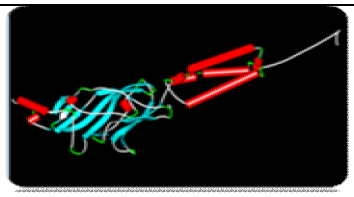
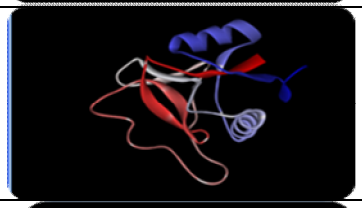
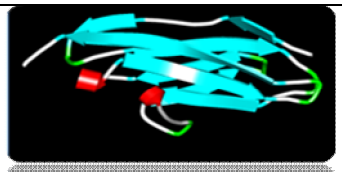
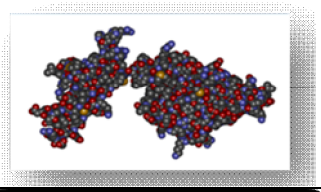
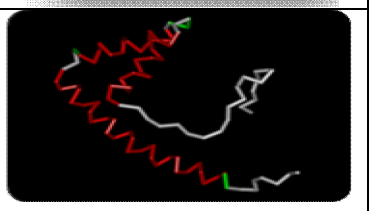
The result of protein –protein docking studies is validated based on the binding affinity values. In this study, the Table 1 clearly shows the binding affinity of species and human cancers. The negatively higher binding affinities are best candidates for cancers. In these results we identify the molecular regions of docking of species proteins and cancer proteins. Table: 4 represent the protein-protein binding scores based on the species proteins are docked with Human cancer proteins. Drug binding affinity were viewed by software such as DISCOVERY STUDIO SOFTWARE and MOLEGRO MOLECULAR VIEWER. Based upon the binding affinity value, the protein C Type Lectin of *Fenneropenaeus indicus* shows that the higher binding affinity value is (-1282.5) - (Table 3) and followed by *Penaeus monodon* (-1169.5) and *Metapenaeus ensis* (-1101.3) for lung cancer gene (CHRNA3). For the blood cancer gene (MLLT10), *Metapenaeus ensis* protein shows higher binding affinity value (-1010.3). *Penaeus monodon* binding affinity (-1013.4) with colon cancer (DCC). Based on the affinities, the proteins (CHRNA3) are best Inhibitors (drug) for human cancer. The retrieved C-type lectin protein sequences of *Fenneropenaeus indicus, Penaeus monodon, Litopenaeus vannamei, Metapenaeus ensis* were docked with the target human cancer proteins such as Lung Cancer, Blood Cancer, Pancreatic Cancer, Breast Cancer and Colon Cancer. The C-type lectin protein of Penaeus species were successfully bound with the human cancer rceptor proteins which show the high binding affinities to the four cancer proteins.

Table 1: Targeted Protein and the Gene with Accession number

Target	protein	NCBI accession	Target	Gene	NCBI Accession
Fenneropenaeus indicus	C-type lectin	ADV17348.1	Blood cancer	MLLT10	CAI39668.1
Penaeus monodon	C-type lectin	ABI97373.1	Lung cancer	CHRNA3	AAH06114.1
Litopenaeus vannamei	C-type lectin	ABI97374.1	Pancreatic cancer	PALLD	AAH13867.2
Metapenaeus ensis	C-type lectin	ABV58637.1	Colon cancer	DCC	EAW62992.1
			Breast Cancer	TOX3	NP_001139660.1

Table 2: 3D structures of the Target Proteins

Target	Protein 3D	Target	Protein 3D
Fenneropenaeusindicus		MLLT10	

Penaeusmonodon		CHRNA3	
Litopenaeusvannamei		PALLD	
Metapenaeusensis		DCC	
		TOX3	

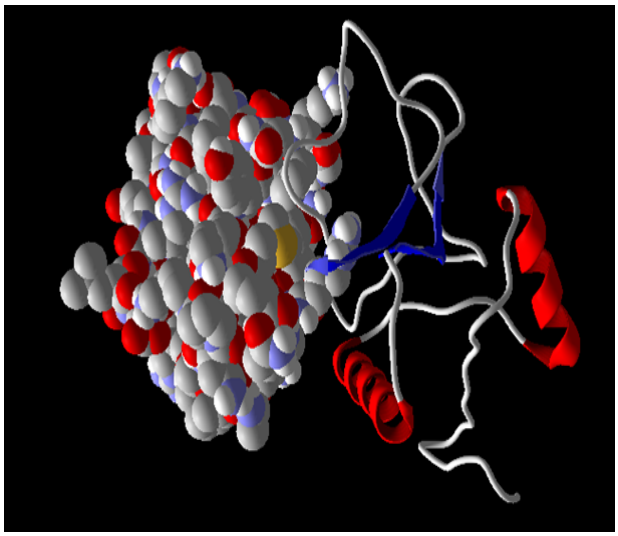


Fig 1: Three dimensional structure of protein -protein complex form. C-type lectin CPK model with atom colors, (CHRNA3)

Table*:* 4 Molecular docking binding affinities against different Cancer proteins

Species	Lung cancer	Pancreatic cancer	Breast cancer	Colon cancer	Blood cancer
Fenneropenaeus indicus	-1282.5	-809.4	-844.8	-958.5	-922.5
Metapenaeus ensis	-1101.3	-739.0	-862.8	-854.5	-1010.3
Litopenaeus vannamei	-130.1	-224.07	-795.5	-947.1	-912.4
Penaeus monodon	-1169.5	-809.5	-825.0	-1013.4	-916.8

DISCUSSION

The current study is an effort to identify the receptor protein that would be consider for the drug development to treat the cancer types. Molecular docking is used to find out the binding orientation of the small molecules against their targets. Thus, molecular docking is considered as important technique in drug designing and screening of novel compounds against this dreadful and challenging diseases [7, 11, 22]. Around 60% of the drugs approved for the cancer treatment are derived from the natural sources [24]. Leila *et al.,*[25] studied with the crab cell extract that inhibited the proliferation of breast cancer cell line. The molecular sequence similarity of C type lectin proteins of Species (*Fenneropenaeus indicus, Penaeus monodon, Litopenaeus vannamei and Metapenaeus ensis*) were applied into the T-Coffee server in order to identify the conserved amino acids present in the protein sequences.

Multiple sequence alignments can also be used to identify functionally important sites, such as binding sites, active sites, or sites corresponding to other key functions, by locating conserved domains [12]. T-Coffee (Tree-based Consistency Objective Function For alignment Evaluation) is a multiple sequence alignment software using a progressive approach. It generates a library of pairwise alignments to guide the multiple sequence alignment. [13]. Our result shows that the C-type lectin protein of the species share 99% sequence homology. The result is a strong evidence to prove that the four species are orthologous. During the study we used 3D structure to predict the species (*Fenneropenaeus indicus* , *Penaeus monodon, Litopenaeus vannamei* and *Metapenaeus ensis*) and human cancer proteins (Lung Cancer, Blood Cancer, Pancreatic Cancer, Breast Cancer and Colon Cancer) using CPH model server. The homology modeling procedure can be broken down into four sequential steps: template selection, target-template alignment, model construction, and model assessment [14]. CPH models-3.0 is a web-server predicting protein 3D-structure by use of single template homology modeling. The server employs a hybrid of the scoring functions of CPHmodels-2.0 and a novel remote homology-modeling algorithm. A query sequence is the first attempted modeled used for fast CPH models-2.0 profile-profile scoring function suitable to close homology modeling [15]. In our research we studied each species docked separately with 5 five types of human cancers and validated the binding energy. The ultimate goal in protein–protein docking is to select the ideal ranking solution based on the scoring scheme that would give an insight into the affinity of the complex. Such a development would drive *in silico* protein engineering, computer-aided drug design and/or high-throughput annotation of which proteins bind or not (annotation of interactome). Several scoring functions have been proposed for binding affinity / free energy prediction [16]. However the correlation between experimentally determined binding affinities and the predictions of nine commonly used scoring functions have been found to be nearly orthogonal ($R^2 \sim 0$) [17]. The initial two steps of this approach were implemented in the Clus Pro 2.0 protein–protein docking server [20, 18, 19].

CONCLUSION

The identified C-Type Lectin molecule can be applied in wet lab protocols which is one of the preliminary step for drug designing against human cancer proteins. The work clearly shows that the *Penaeus* species having best pharmacological potentials proteins. Besides its dietary economical and the proteins of (*Fenneropenaeus indicus, Penaeus monodon, Litopenaeus vannamei and Metapenaeus ensis*) were successfully bound against the receptor proteins of the human cancer (Lung Cancer, Blood Cancer, Pancreatic Cancer, Breast Cancer and Colon Cancer). In future these results pave way for drug designing against the dreadful cancer.

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