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IN-SILICO DRUG DESIGNING AND DOCKING STUDIES ON RIBONUCLEOSIDEDIPHOSPHATE REDUCTASE – LARGE SUBUNIT 1 (RRM 1) PROTEIN

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ABSTRACT

Globally, cancer remains a mammoth burden as it mounts the second major cause of mortality. Heterogeneity of Cancer remains to be a daunting challenge and makes the oncological researcher to keep bustling under active investigation. There are several chemo drugs used in the treatment of cancer. Still oncologists seek a better and more effective drugs for enhanced therapy. The present in-silico study focuses on designing a new anti-cancer drug molecule. The designed drug was docked against the target protein, Ribonucleoside-diphosphate reductase large subunit 1 (RRM 1). Several Bio-informatics software were utilized to perform this investigation. In general, antioxidant molecules possess the cancer preventing as well as the cancer fighting properties. Few natural compounds with high antioxidant activity were opted and combined with the potential and existing drug, Gemcitabine. Cheminformatics software was employed to design four different drug molecules. In-silico pharmacokinetic study was performed. The bio-activity scores, molecular properties score and drug likeness was elucidated with Molinspiration. Both the designed drugs and existing drug were docked against the target protein. Compound 1 was found to exhibit the stable conformation with the highest affinity binding scores of -310.78Kcal/Mol. The existing drug shows the affinity binding score of -178.65 Kcal/Mol. On the other hand, all the four designed drugs exhibit good affinity binding scores when compared to the existing drug.

Keywords: Cancer, Cheminformatics, Gemcitabine, PUFA and In-silico docking

INTRODUCTION

Every year, Cancer Registry Programme of both developed and developing countries estimates the incidence of new cancer cases and cancer caused mortality to provide statistics. Approximately, one sixth of fatality is due to cancer **[1]**. Breast cancer, lung cancer, colon and rectal cancer, prostate cancer, bladder, kidney and renal cancer, and pancreatic cancer are the most common forms of cancer reported in United Statesand India **[2, 3]**. Mortality rate of such cancer forms are found higher than any other forms. Oncologists thus remain hard-pressed under active investigation.

Gemcitabine is an FDA approved conventional drug used as afirst-line treatment for pancreatic cancer, advanced ovarian cancer, Non-Small Cell Lung Carcinoma (NSCLC), metastatic breast cancer and bladder cancer. Gemcitabine is a nucleoside analogue of deoxycytidine. It inhibits the Ribonucleoside-Diphosphate Reductase Large Subunit 1 (RRM 1) protein, which is one of the key enzymes that metabolizes the synthesis of deoxyribonucleotides from the respective ribonucleotides **[4]**. It is a well-knownanti-tumour drug that are recognized to induce apoptosis of wide range of malignant cell in both in-vitro and in-vivo studies. This drug interrupts the cell cycle of various forms of malignant cell at G1/S boundary phase **[5]**. Gemcitabine is thus found to be a potential drug against advanced forms of cancer. On the other hand, long chain poly unsaturated fatty acids are popularly known to be anti-oxidant molecules and are as always, an inevitable substance to mankind. These potential antioxidant molecules also act as an anti-cancer adjuvant. Docosahexaenoic acid is highly efficient to ameliorate the activities of convectional anticancer drugs. It is achieved by increasing the uptake of drug as well as prompt apoptosis of tumour cells by altering the oxidative level and suppressing the progression of carcinoma **[6]**.

In this research, the convectional anticancer drug Gemcitabine was coupled with four different antioxidant molecules respectively using cheminformatics. This computer aided drug designing tool remains preferable and recommended, as it aids to acquire knowledge about newly designed drugs without any side effects. We focussed on drug designing and docking the same against RRM1, as anti-cancer targets.

MATERIALS AND METHODS

Retrieval of advanced anticancer drug data

National Cancer Institute's website was utilized to collect information about the anti-cancer drugs **[7]**. The drug bank databases were further exploited to gather

details about the conventional anti-cancer drugs used infirst line treatment **[8]**.

Modelling and visualization of target protein

The amino acid sequence of the target protein was retrieved from Protein Data Bank **[9]**. An accurate and flawless 3D model of the target protein was predicted by employing CPH server model 3.0 **[10]**. It is an automated homology modelling server with high-speed performing 3D prediction tool. The 3D structure was visualized by a molecular visualizer tool, Accelrys Discovery Studio software V2.5.

Drug designing and its validation

Four different and most essential fatty acids of both omega 3 and omega 6 with high antioxidant activity were selected and combined separately with Gemcitabine, anti-cancer drug molecule. Newly designed 4 drug molecules were designed and validated using Molinspiration **[11]**. It's a cheminformatics software used to validate the molecular properties and bioactivity of the designed drug candidate.

Drug docking and 3D visualization

Patch Dock was adopted for flexible docking **[12]**. It's an automated molecular drug docking server. The designed drugs and the control molecule were docked against the target to find out the drug binding scores. Discovery studio software was employed to generate the 3D maps of protein-drug interaction.

RESULTS AND DISCUSSION

The target RRM1 structural gene was present in chromosome 11, band p15.4. The gene transcript was found to be longest with a sequence of 3142 nucleotides comprising 20 exon counts. It encodes an essential enzymes of length 792 amino acids with a molecular weight of 89939 Da. CPH models 3.0, the remote homology modelling server predicted the three-dimensional form of RRM1 the target protein. The predicted 3 D structure was visualized using Discovery Studio software **(Figures 1)**. The intramolecular structural properties of the above predicted secondary structure of the target protein and both properties and arrangements of amino acids play a key role in the structure-based drug designing method. Similarly, 3 D form of Gemcitabine was visualized **(Figure 2)**.

Molinspiration, an advanced cheminformatics software validated the accurate values of bioactivity scores, molecular properties score and the drug likeness scores for all the four designed drug molecules. Patch Dock server uses an advanced and significant logarithm to dock the protein and the drug **[13, 14]**. The in-silico docking output of RRM1 with the existing and designed drugs were tabulated **(Table 1)**. The Atomic Contact Energy (ACE) value indicates binding affinity scores of the

Drug – target protein interaction. Compound 1 shows the lowest ACE value. It implies a lower desolvation free energy. Hence it is considered to be more favourable. All the 4 designed drugs showed the higher negative values when compared with the existing drug. This in-silico study has suggested that our designed drug molecules are more efficient than the existing drug candidate for the protein target RRM1, which is highly expressed in malignant cells and remains the major cause for the uncontrolled replication of cancerous cells. Ultimately the designed drug molecules have potential to inhibit the RRM1 protein and thus arrest the cell cycle and promote apoptosis.

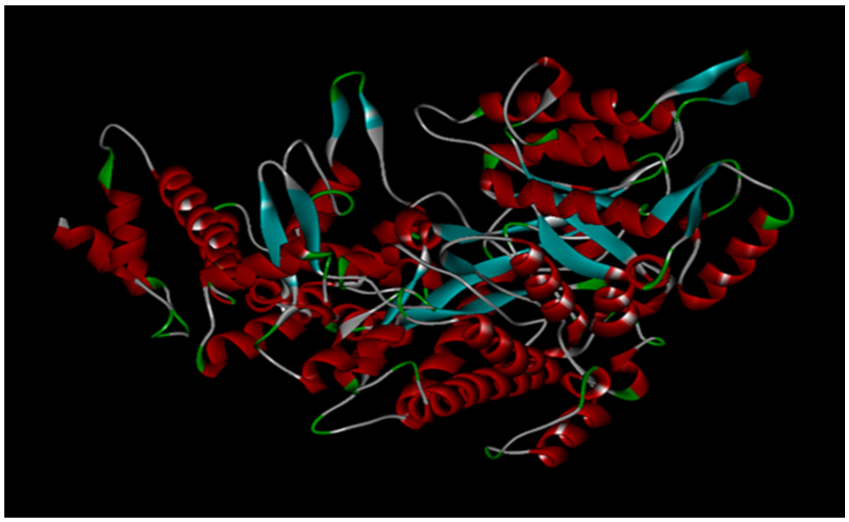


Figure 1: 3-Dimensional form of Secondary structure of Ribonucleoside diphosphate reductase large subunit1 protein. The red colour represents the αhelices, blue colour – β sheets, green – turns and white indicates the turns

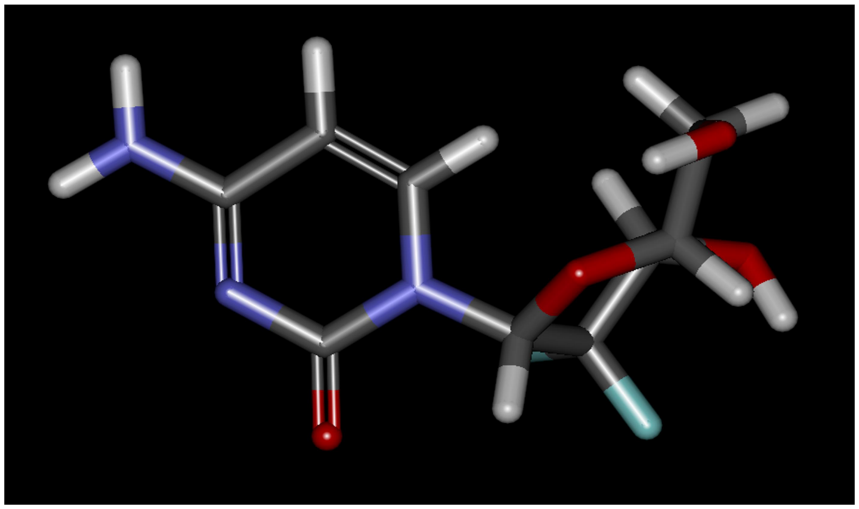
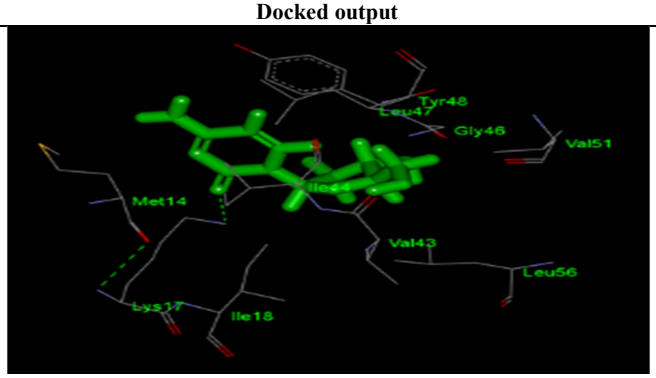
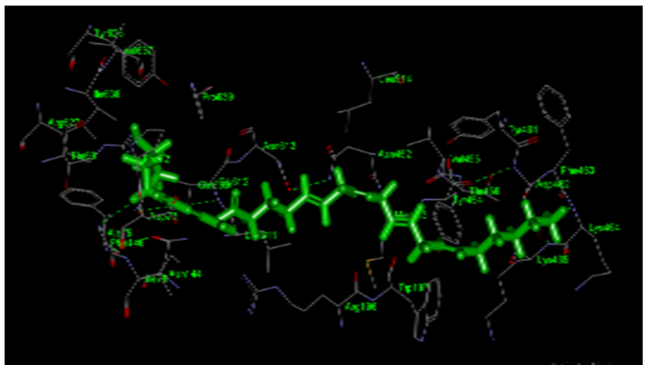
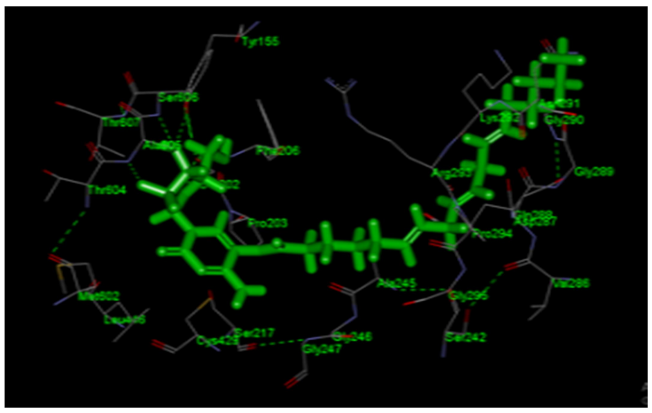
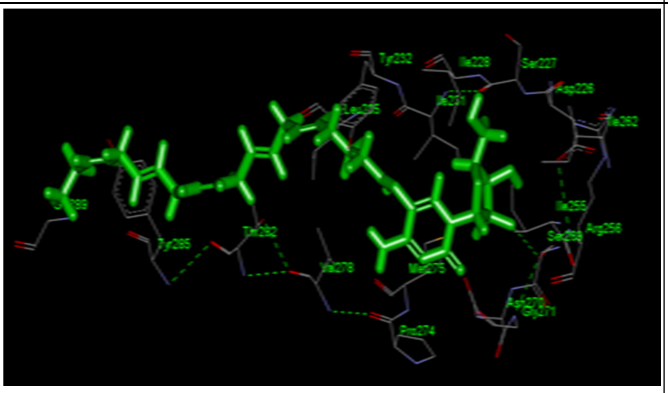
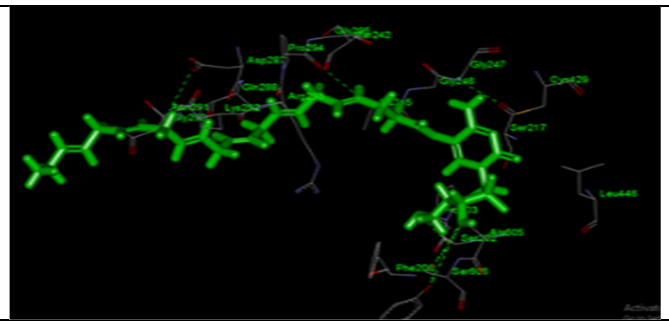


Figure 2: 3-Dimensional form of Gemcitabine. Grey colour indicates carbon, white- hydrogen, blue -nitrogen and red-oxygen

Table 1: In-silico molecular docking: ACE - Atomic Contact Energy

S. No.	Drug	Docked output	ACE (Kcal/Mol)
1.	Existing Drug- Gemcitabine		-178.65
2.	Compound 1		-310.78
3.	Compound 2		-303.64
4.	Compound 3		-294.77
5.	Compound 4		-280.03



Compound 1 – Gemcitabine+ all-cis-5,8,11,14 eicosatetraenoic acid;
Compound 2 – Gemcitabine + all-cis-6,9,12-octadecatrienoic acid;
Compound 3 – Gemcitabine + all-cis-5,8,11,14,17 eicosapentaenoic acid;
Compound 4 – Gemcitabine + all-cis-4,7,10,13,16,19 docosahexaenoic acid.

CONCLUSION

In this present investigation, four different potent anti-cancer drug molecules were designed and complete in-silico pharmacokinetics has been validated. The docking studies revealed the good affinity binding scores between the four designed drug candidates and the protein target. The conformation of the docked compounds was found to be more stable. The pharmacokinetic study suggested that all the four designed drug candidates are safe. Therefore, the designed drug candidates are taken for further investigation with various forms of cancer cell lines and animal model studies.

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