Application of Genetic Algorithm in Understanding Drug-Drug Interactions

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ABSTRACT: *Genetic algorithms (GA) are promising search algorithms in virtual screening of drug-discovery process. A molecular docking tool extensively used in the process of drug discovery uses GA as search algorithm. CYP2B6 is an important drug metabolizing enzyme in the super family of CYP enzymes but less understood and polymorphic in nature. Anticancer drugs Cyclophosphamide and Thiotepa are both metabolized by CYP2B6. The present work embodies the impact of Single Nucleotide Polymorphism(SNP) of CYP2B6 enzymes on drug-drug interactions of anti-cancer drugs Cyclophosphamide and Thiotepa when both are administered concurrently in terms of binding energies by molecular docking using "ArgusLab" . The outcome of the present work may find its application in pharmacogenomics which holds a promise in personalized medicine that drugs might one day be tailor-made for individuals and adapted to each person's own genetic makeup.*

Keywords: receptor, ligand, active site, molecular docking, binding energy, polymorphism, virtual screening

I. INTRODUCTION

Genetic Algorithms (GA) are dominant tools in difficult search optimization problems. The GA works with a population of encoded individuals where each individual represents a possible solution for the problem to be solved. The fitness or goodness of each individual is calculated using objective function. Based on some fitness criteria, some of the individuals will be selected to undergo crossovers resulting in offspring. Offspring based on certain rules may replace the old population. This cycle of selection, crossover and replacement repeats to evolve better and better individuals. Thus, GA is a heuristic search that imitates the process of natural evolution and generates useful solutions to search optimization problems [1]. GAs are used to tackle wide variety of problems. One of the important applicatons of GA is in virtual screening of drug-discovery and development process [2].

The drugs that enter the human body tend to stimulate certain receptors mostly made up of proteins in the human body. The interaction of drug (ligand) with the amino acids in the active site of protein (receptor) is called as drug binding or docking . When a drug binds to a receptor, it results in the change of conformation of the three dimensional structure of the receptor leading to change in the receptor or protein functions in the body. Hence an understanding of binding interactions between receptor and ligand is very important for drug discovery scientists. Computational methods such as molecular docking speeds up the process of understanding the binding interactions. The strength of binding interactions can be understood in terms of binding energies. Among the various molecular docking tools available, ArgusLab is one of the important tools used in the process of drug discovery. Search algorithm and scoring functions are two important components of any molecular docking tool. Search algorithms are used to generate various poses of the ligand in the active site of the protein and scoring function scores poses which are near to experimentally determined ones. ArgusLab uses GA as search algorithm [3,4,5].

There are many receptors in the human body which metabolize drugs of which CYP enzymes are of utmost importance. These enzymes are found to be polymorphic in nature which may have an impact on drug metabolism [6,7]. For certain diseases, two or more drugs are administered simultaneously. In such cases, one drug may interact with another drug if both the drugs are metabolized by the same enzyme. Hence an understanding of the drug-drug interaction and the effect of variations in genes of the receptor on drug-drug interactions in terms of binding energies will be helpful in successful design and discovery of more efficient drugs. Therefore, in the present work effect of polymorphism of drug metabolizing enzymes on drug-drug interactions is studied using a molecular docking tool "Argus Lab" which uses GA as search algorithm.

II. METHODS

In the present work CYP2B6 which is a less understood polymorphic enzyme of CYP family is chosen as receptor and anti-cancer drugs Cyclophosphmide and Thiotepa which are administered concurrently and both metabolised by

CYP2B6 enzymes are used as ligands [8,9,10,11,12,13,14,15,16,17]. For all molecular docking studies, structures of ligands and receptor are rudimentary. 2D structures of the ligand are downloaded from PubChem database of NCBI (National Centre For Biotechnology Information) and are displayed below.
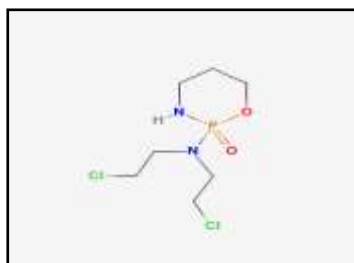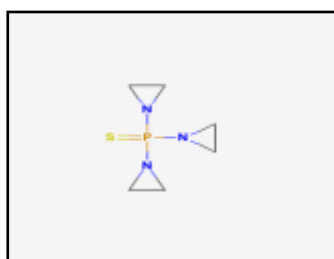

Figure 1 : 2D Structure of Cyclophosphamide

Figure 2 : 2D Structure of Thiotepa

2D retrieved structure of ligands are converted to 3D mol file through Online SMILES Translator And File Generator tool. Further cleaning of ligands are done by selecting "Clean hybridization option of ArgusLab 4.0.1". 3D structure of the receptor CYP2B6 WildType (without polymorphism) is procured from the NCBI structure database and is as displayed below. It is cleaned further by the researchers with the help of SWISS-Pdb Viewer tool to remove hetatoms of CYP2B6 WildType .
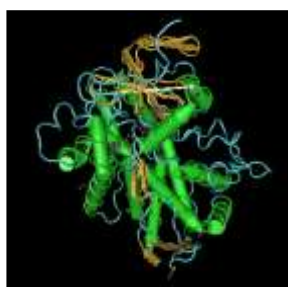

Figure 3: 3D Structure of CYP2B6 WildType

Various polymorphs, mainly Single Nucleotide Polymorphs (SNP) of CYP2B6 are reported in the database dbSNP of NCBI. Among them five SNPs which are chosen randomly for current study are displayed below.

S.No	Amino Acid Position	Amino Acid Replacement
1	22	R with C
2	172	Q with H
3	259	S with R
4	262	K with R
5	487	R with C

Table 1 : SNPs selected for present study

The structures of the above chosen SNPs of CYP2B6 are also essential for carrying out molecular docking. But these structures are not available in the NCBI structure database. Therefore, 3D structures for SNPs are constructed by the researchers using Homology Modeling [18] which henceforth are referred as receptors SNP 22, SNP 172, SNP 259, SNP 262, SNP 487. Knowing the active site of the target protein is of crucial importance to docking as binding of small molecule occurs at binding site or active site of the target. The active site can be found from PDB files or from literature survey. The authors in this work have found the active site of CYP2B6 from the literature survey [19] which consists of the residues mentioned below in the Table 2.

Phe206, Ala298, Thr302, Leu363 or heme pocket;	for pocket A
Ile114, Phe115, Ser294, and Phe 297	for pocket B
Ile209, Val367, and Val477	for pocket C)

Table. 2: CYP2B6 Active site Residues

Subsequently, molecular docking is carried out using "ArgusLab". Docking is performed using the "Dock a ligand" option under the "calculation" menu. A spacing of 0.4 Å between the grid points is used. "Dock" is chosen as the calculation type, "flexible" for the ligand and the AScore is used as the scoring function. A maximum of 150 poses are allowed to be analyzed and binding site box size is set to 20 x 20 x 20 angstroms so as to encompass the entire active site. The AScore function, with the parameters read from the AScore.prm file is used to calculate the binding energies of the resulting docked structures [20].

III. RESULTS AND DISCUSSIONS

The study of drug-drug interactions between Cyclophosphamide and Thiotepa is done under two different situations. In the first situation, Cyclophosphamide is docked first to the active site of CYP2B6 WildType (receptor) and

binding energy of the intermolecular complex is determined. Then Thiotepa is also docked to the active site of the receptor which has the ligand (Cyclophosphamide) bound and binding energy is determined. The difference in binding energy of the intermolecular complex before docking Thiotepa and after docking Thiotepa are tabulated

Receptor	Binding Energy of Cyclophosphamide, K Cal/mole		Binding Energy Differences In K cal/mol
	Before Docking Thiotepa	After Docking Thiotepa	
CYP2B6 WildType	-6.38077	-6.30973	-0.07104
SNP 22	-6.3131	-6.3131	0
SNP 172	-6.32698	-6.32698	0
SNP 259	-6.3251	-6.3251	0
SNP 262	-6.37855	-6.37855	0
SNP 487	-6.33842	-6.33842	0

Table 3: Binding Energy differences before and after docking Thiotepa

In the second situation, Thiotepa is first docked to the active site of CYP2B6 WildType and the binding energy of the intermolecular complex is determined. Subsequently Cyclophosphamide is also docked to the same active site of the receptor which has the ligand (Thiotepa) bound and binding energy is determined. The difference in binding energy of the intermolecular complex before docking Cyclophosphamide and after docking Cyclophosphamide are tabulated.

Table 4: Binding Energy differences before and after docking Cyclophosphamide

Receptor	Binding Energy of Thiotepa, K Cal/mole		Binding Energy Difference in K cal/mole
	Before Docking Cyclophosphamide	After Docking Cyclophosphamide	
CYP2B6 WildType	-5.06156	-5.06156	0
SNP 22	-5.05922	-5.05955	0.00033
SNP 172	-4.89492	-4.92245	0.02753
SNP 259	-5.05154	-5.05154	0
SNP 262	-4.92188	-4.92188	0
SNP 487	-4.97902	4.97902	0

From Table 3 , with CYP2B6 WildType as receptor, a difference in binding energy is recorded before docking Thiotepa and after docking Thiotepa. But in case of SNPs, Thiotepa does not have any effect on Cyclophosphamide as binding energy difference of Cyclophosphamide with and without Thiotepa is zero as shown in the Table 3.

From Table 4, in case of WildType receptor, Cyclophosphamide does not have any effect on Thiotepa. But in case of SNP 22 and SNP 172 energy of Thiotepa becomes less after docking Cyclophoosphamide. In both the cases, Thiotepa has a higher binding affinity in the presence of Cyclophosphamide. For other receptors Cyclophosphamide does not have any effect on Thiotepa .

IV.   CONCLUSIONS

In the present study, drug-drug interactions and influence of SNPs on drug-drug interactions is understood interms of binding energies using "ArgusLab" a molecular docking tool which uses GA as a search algorithm. Binding energy differences are found when Cyclophosphamide and Thiotepa are administered simultaneously. Thus Cyclophosphamide and Thiotepa both being metabolized by CYP2B6 enzymes and binding to the same active site, each drug may have a profound impact on the metabolism of the other. We can conclude that when two drugs are metabolized by the same enzyme and bind to the same active site depending upon the gene make up of an individual , there is possible drug-drug interaction because of which one drug may alter the efficacy of the other. This implies that medical treatments have to be tailored according to the gene make up of an individual. Hence the present study has made a contribution to the emerging personalized medicine field.

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