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In Silicopharmacological Evaluation of Beta Carotene for Its Anti-Bacterial, Anti Diabetic, Anti-Oxidant, Anti-Cancer Activities

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ABSTRACT
Drug design is the inventive process of finding new medications basedon the knowledge of a biological target. The major aim is to findwhether the given molecule bind to the target and causespharmacological actions or not.The compound wascomputationally designed and optimized with the docking toinvestigate the interaction between the target protein and ligand. The anti-oxidant, anti-diabetic, anti-bacterial, anticancer activities of beta carotene was evaluated by using insilico pharmacological study. This was investigated by molecular docking using the auto dock software.Among these entire beta carotene compound have more binding energyvalues. Here we also studied the molecular properties of beta carotene compound usingmolinspiration software.
KEYWORD:Beta carotene, Tyrosinase, Docking,Autodock,RCBS Protein data bank.

I. INTRODUCTION

The drug is most commonly an organic small molecule that activates or inhibits the functionof a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient.In the most basic sense, drug design involves the design of molecules that are complementaryin shape and charge to the bimolecular target with which they interact and therefore will bind to it. This type of modeling is sometimes referred to as computer-aided drug design.

Drug discovery process begins with the identification of a possible therapeutic target. Theselected ligand target must be a key molecule involved in a specific metabolic or cell signalingpathway that is known or believed to be related to a particular disease state. β-Carotene is the more common form and can be found in yellow, orange, and green leafy fruits and vegetables. As a rule of thumb, the greater the intensity of the orange colour of the fruit or vegetable, the more β-carotene it contains. β-Carotene is an organic, strongly colored red-orange pigment abundant in fungi, plants, and fruits. It is a member of the carotenes, which are terpenoids (isoprenoids), synthesized biochemically from eight isoprene units and thus having 40 carbons. Among the carotenes, β-carotene is distinguished by having beta-rings at both ends of the molecule. β-Carotene is biosynthesized from geranylgeranyl pyrophosphate.

II. MATERIALS & METHOD:

For this present study we have used bioinformatics tools, biological databases like PDB(Protein Data Bank) and software's like auto dock and ACD ChemSketch. The PDB is thesingle worldwide archive of structural data of biological macromolecules, established inBrookhaven National Laboratories (BNL). It contains structural data of the macromoleculeresolved by X-ray crystallographic, NMR methods etc. auto dock is an automated dockingtool. It is designed to estimate how small molecules such as substrates bind to a receptor ofknown 3D structures.

III. RESULT AND DISCUSSION

Molecular Docking Studies

In order to gain more insight on the binding mode of compound with E.coli enoyl reductase (1C14),alpha amylase(1UA7), Tyrosinase (3NM8) and Hexokinase 2 (NZT) dockingstudies using auto dock 4.0.2 were carried out. Topscoring molecule from the largest clusterwere contemplate for interaction studies. The crystallographic structure of E.coli enoyl reductase

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(1C14),alpha amylase(1UA7), Tyrosinase (3NM8) and Hexokinase 2 (NZT) which isrepossess from the RCSB protein databank (PDB code 3NM8) serve as docking receptor andβ-Carotenewas elected as ligand molecule. Before docking the disguiseligand into the protein active side, the protein was prepared by deleting the substratecofactor as well as the crystallographically observed water molecules and then protein wasdefined for generating the grid. The structure of β-Carotene were drawn using ChemDraw Ultra 8.0 andenergy minimized using Chem 3D Ultra 8.0 software.

Auto Dock 4.0.1 Procedure

Automated docking was used to search out the appropriate binding orientations and conformations of various inhibitors into the 3NM8 binding pocket. To perform the task, the powerful genetic algorithm method implemented in the program Auto Dock 4.0.1 was employed. Grid maps were generated by Auto Grid program. Each grid was centered at the crystal structure of the corresponding 1G2A and 2GT1 separately. Lamarckian genetic algorithm was employed as the docking algorithm. The grid dimensions were60 Å X 60 Å X 60 Å with points separated by 0.375Å. For all ligands, random starting positions, random orientations and torsions were used. During docking, grid parameters were specified for x, y and z axes as 38.808, 30.946 and 42.249 respectively. The docking parameters number of genetic algorithm (GA) runs: 25, population size: 150, maximum number of evaluations: 2,500,000, maximum number of generations: 27,000 were used for this study. The structure with the lowest binding free energy and the most cluster members was chosen for the optimum docking conformation.

Calculation of Molecular Properties

The molecular properties were calculated on the basis of simple molecular descriptor used by "Lipinski's rule of 5".The five properties consist of molecular weight, hydrogen bond donor, hydrogen bond acceptor, Log P, total polar surface area(TPSA) which was calculated using the online cheminformatics tool molinspiration (https://www.molinspiration.com/) 18 and the result were Table 1

Table 1: Molecular descriptor properties of Beta Carotene & Standard drugs

Compoud Name	Log P	Molecular weight	Hydrogen acceptors	Hydrogen donors	No. of violation
Beta Carotene	9.8	536.89	0	0	2
Triclosan	5.31	289.55	2	1	1
Acarbose	5.51	645.61	19	14	3
NDGA	3.48	302.37	4	4	0
5-Flurouracil	-0.59	130.08	4	2	0

Drug likeness Properties of Designed Isoxazole Derivatives

The molinspiration virtual screening is fast (100,000 molecules may be screened in about 30 minutes) and therefore allows processing of very large molecular libraries. Validation tests performed on various target classes (including kinase inhibitors, various GPCR targets, different enzymes etc.,) show 10 to 20- fold increases in hit rate in comparison with standard / random selection of molecules for screening. The data's for drug likeness properties were depicted in **Table 2**.

Table 2: Drug likeness properties of designed compounds

Compound Name	GPCR Ligand	Ion channel Modulator	Kinase Inhibitor	Nuclear Receptor Ligand	Protease Inhibitor	Enzyme Inhibitor
Beta carotene	-0.04	-0.15	-0.15	0.40	-0.06	0.17
Triclosan	-0.18	-0.18	-0.14	-0.07	-0.43	0.01
Acarbose	-0.02	-0.49	-0.33	-0.29	0.21	0.21

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NDGA	0.03	0.11	-0.05	0.14	0.01	0.13
5-Flurouracil	-2.60	-1.95	-2.62	-3.04	-3.15	-1.56

DOCKING ANALYSIS:

The docking results of E.coli enoyl reductase (1C14),Alpha amylase (1UA7), Tyrosinase (3NM8) and Hexokinase 2 (2NZT)with the Beta carotene as ligand and standard drugs are reported in the Table 3 and Table 4. The best docked structures should have lower binding energies. The binding sites and the active sites are shown in the snapshots. The crystal structure of the E.coli enoyl reductase (1C14),Alpha amylase (1UA7), Tyrosinase (3NM8) and Hexokinase 2 (2NZT)protein was derived from PDB and used as a target for docking simulation shown.

Fig 1: Enoyl reductase E.coli (1C14)

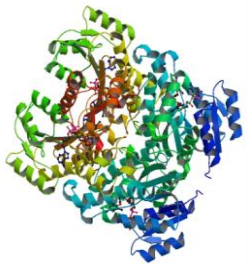


Fig 2: Alpha amylase (1UA7)

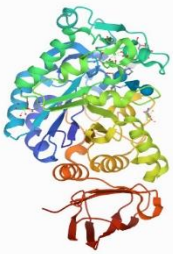


Fig 3: Tyrosinase (3NM8)

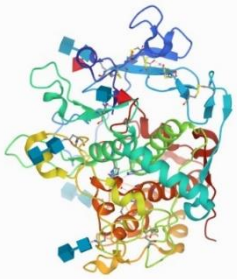
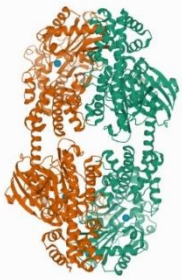


Fig 4: Hexokinase 2 (2NZT)



The compound Beta carotene was selected from the literature reviews and the structures of ligand (Beta carotene) are drawn using Chem sketch and determined the drug likeness properties. Ligand were created and prepared for the lead optimization and docking procedure using Chem sketch, molinspiration and auto dock.

Binding site of the protein:

1. Enoyl reductase E.coli NAD+ (1C14):
GYP51, TYR76, ARG96, ALA256, THR260, HEM460

2. Alpha amylase (1UA7)
ASP212A, YS179A, ASN273A, TYR59A, GLn63A, Gln126A, Leu142A, HIS180A

3. Tyrosinase (3NM8)
LYS47A, LYS47B, GLU141A, ALA40A, GLY143A, ALA44B and ILE139A

4. Hexokinase 2 (2NZT)
TYR334, PHE330, PHE331, PHE288,TRP279, SER288, LE287

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Binding of Triclosan& Beta carotene with Enoyl reductase E.coli NAD+ (1C14)

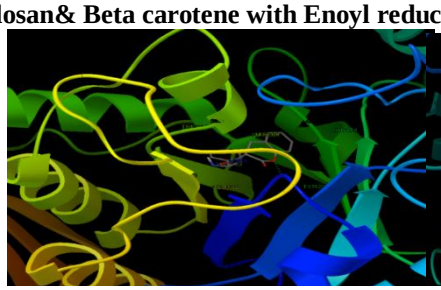

Fig5.Triclosanbinding with 1C14

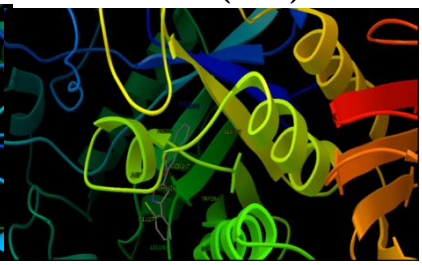

Fig 6.Beta carotene binding with 1C14

Binding of Acarbose& Beta carotene with α-amylase enzyme (1UA7)

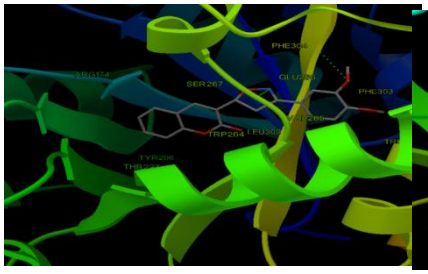

Fig 7.Acarbose binding with 1UA7

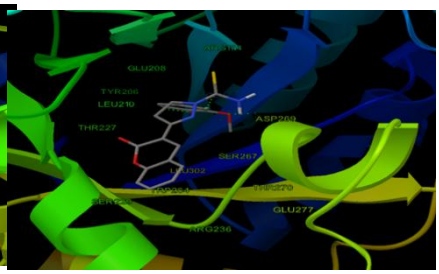

Fig 8. Beta Carotene binding with 1UA7

Binding of Nor dihydroguaiaretic acid (NDGA) & Beta carotene Tyrosinase enzyme (3NM8)

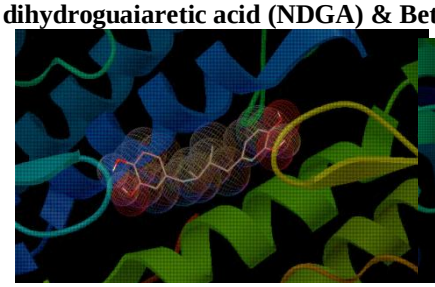

Fig9. NDGA binding with 3NM8

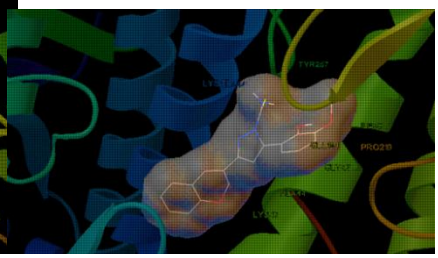

Fig 10.Beta Carotene binding with 3NM8

Binding of 5-Flurouracil& Beta carotene with Hexokinase 2 2NZT

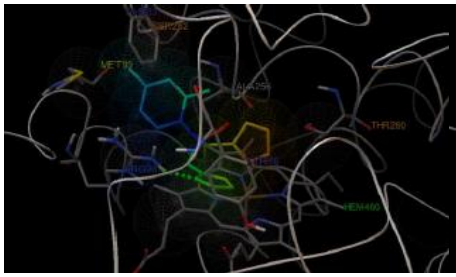

Fig 11.5-Flurouracil with 2NZT

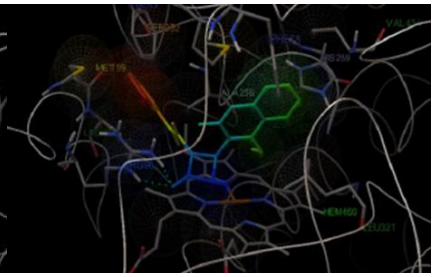

Fig 12.Beta Carotene with 2NZT

Table 3: Energy minimization table

Target Protien	Code	Binding Energy (Kcal/mol)	Inhibition Constant	Vdw. Desolvation Energy	Interm ol Energy	Ligand efficiency	Electro static Energy	Total internal
Enoyl reductase E.coli	Beta Carotene	-16.64	113.5	-7.22	-7.24	-0.29	-0.02	-0.25
	Triclosan	-10.39	111.05	-5.77	-5.99	-0.32	-0.22	-0.45

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NAD+								
α-amylase enzyme (1UA7)	Beta Carotene	-26.21	103.7	-8.66	-6.42	-0.92	-0.01	-0.35
	Acarbose	-21.67	122.7	-7.65	-6.88	-0.42	-0.02	-0.55
Tyrosinase (3NM8)	Beta Carotene	-19.27	1.36	-8.66	-8.6	-0.36	0.06	-0.29
	NDGA	-18.01	137.95	-5.77	-5.86	-0.53	-0.09	-0.17
Hexokinase 2 (2NZT)	Beta Carotene	-10.33	122.63	-9.76	-5.6	-0.25	0.09	-0.32
	5-Fluroura cil	-18.97	145.23	-7.55	-3.66	-0.65	-0.07	-0.23

IV. CONCLUSION

- The present study establishes that computational tools help in minimizing the tedious process of drug discovery and delivers new drug candidate more quickly.
- The Protein-Ligand interaction plays a significant role in structural based designing. In the present workwehave taken the ligand Beta Carotene moiety and identified itsAnti-bacterial activity, Anti-diabetic activity, Anti-oxidant activity, and Anti-cancer activity by docking analysis.
- E.colienoylreductase (1C14), Alpha amylase (1UA7), Tyrosinase (3NM8) and Hexokinase 2 (2NZT) enzymeswas selected as target and by literature review Beta carotene was selected as lead molecule.
- The drug likeness score established the compounds to be pharmacokineticallyactive

Compounds Beta carotene as ligand exhibited maximum E.colienoylreductase (1C14), Alpha amylase (1UA7), Tyrosinase (3NM8) and Hexokinase 2 (2NZT)enzymes inhibitory activity, by docking analysis using auto dock software.

- In this, molecular docking was applied to explore the binding mechanism and to correlate its docking score with the activity ofTriclosan, Acarbose, NDGA and 5-Flurouracil compounds. The results of our present study can be useful for the design and development of beta carotene having better inhibitory activity against several type of Anti-bacterial activity, Anti-diabetic activity, Anti-oxidant activity, and Anti-cancer activity.This potential agent will be a promising candidate can further be validated in wet lab studies for its proper function.
- Among the binding scores with different target proteins, Beta carotene with hexokinase 2 inhibition shows which may produce anti-cancer activity also with anti-bacterial, anti-diabetic and anti-oxidant activities can be taken for further studies as the lead molecule and acute toxicity studies are to be done on these promising compound.

V. ACKNOWLEDGEMENT

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