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Research Article

MOLECULAR DOCKING AND BIOAVAILABILITY STUDIES OF CAFFEINE AND CAFFEIC ACID COMPOUNDS WITH APOPTOSIS REGULATED PROTEINS

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ABSTRACT

Oral squamous cell carcinoma is the most common type of oral cancer accounting for almost 90 % of all oral malignancies, around 20 % of cancer burden in India. Caffeine and caffeic acid widely present in many fruits, vegetables, coffee and these compounds having various proved pharmacological health benefits to human. In this study, we investigate the selected apoptotic regulated proteins (receptors) mutant p53, Bcl-2, Bax and casapase-9 from human origin, which is actively involving in oral cancer signaling. The receptors were docked to the caffeine and caffeic acid and the energy value obtained as follows using the Hex 6.0 docking software. These compounds have better bioavailability (ADME) and receptor and ligand interaction leads to involves in apoptosis signaling related to oral cancer.

Keywords: Caffeine, Caffeic acid, apoptosis regulated proteins, Molecular docking

INTRODUCTION

Oral cancer is a subtype of head and neck cancer is any cancerous tissue growth located in the oral cavity[1]. There are several types of oral cancers, but around 90 % are squamous cell carcinomas, originating in the tissues that line the mouth and lips and cheek lining[2]. Epidemiological studies have shown that chewing of betel quid with tobacco; smoking is the major etiological factor of oral carcinogenesis in India[3]. The largest data on buccal mucosa cancers is from India and 70 % - 80 % of the patients with buccal mucosa cancers are locally advanced at the time of presentation. There are few studies on induction chemotherapy or concurrent chemotherapy from India in any randomized settings in head and neck cancer patients including buccal mucosa cancer and large retrospective study[4,5]. Computational Biology and bioinformatics have the potential not only of speeding up the drug discovery process thus reducing the costs, but also of changing the way drugs designed. Rational Drug Design (RDD) helps to facilitate and speed up the drug designing methods, which involves variety of methods to identify novel compounds[6]. The concept of docking and bioavailability is important in the study of various properties associated with protein-ligand interactions found to be lying deep into the binding cavity of the enzyme exhibiting all the major interaction such electrostatic interactions binding energy and electron distribution[7]. This was followed by ADME-Toxicity prediction (absorption, distribution, metabolism, and toxicity) of the docked compounds to evaluate its properties to be an orally active compound. In this study we investigate the caffeine, caffeic acid are important antioxidant dietary compounds used to analysis bioavailability scores and molecular docking with selected apoptosis signaling proteins mutant p53,Bcl-2,Bax, and Caspase-9.

MATERIALS AND MTHODS

Preparation of ligand structures

Caffeine (CID 2519) and caffeic acid (CID 689043) structure and smiles were retrieved from Pubchem database. Bioavailability scores of compounds predicted by molinspiration are cheminformatic. Such methods have seen frequent use in the discovery and optimization of novel molecules with affinity to a target, the clarification of absorption, distribution, metabolism, excretion and toxicity properties as well as physicochemical characterization[8].

Molinspiration-cheminformatics software tool

Molinspiration offers broad range of cheminformatics tool[9] (Molinspiration Cheminformatics, Slovensky Grob, Slovak Republic) software tools supporting molecule manipulation and processing, including SMILES and SD file conversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties and bioavailability.

Preparation of protein structures

Availability of several experimentally determined three-dimensional structures of mutant p53 [BAC16799.1], Bcl-2 [P10415.2], Bax [Q07812.1] and Caspase-9 [P55211.3] from human origin, Co crystallized with various inhibitors provides excellent basics for using structure-based approaches for the discovery of new inhibitors. These selected proteins sequences retrieved from NCBI database as a FASTA format.

Protein homology modeling using Swiss-model server

SWISS-MODEL is a structural bioinformatics web-server dedicated to fully automated homology modeling of protein 3D structures. It assists and guides in building protein

homology models at different levels of complexity. To used this server in this study for modeling of selected proteins.

Protein-ligand interaction using Hex 6.0

The homology-modeled 3D protein structure retrieved from the Swiss model applied into the by HEX docking software for caffeine and caffeic acid compounds docking with proteins. Hex is an interactive molecular graphics program for calculating and displaying feasible docking modes of protein and DNA molecules. Hex cal also calculates protein-ligand docking, assuming the ligand is rigid, and it can superpose pairs of molecules using only knowledge of their 3D shapes. It uses spherical polar fourier (SPF) correlations to accelerate the calculations and its one of the few docking programs which has built in graphics to view the results.

Table 1: Drug likeness properties of caffeine and caffeic acid molinspiration cheminformatic tool

S. No	Properties	Caffeine	Caffeic acid
1.	Log p (Octanol-water partition Coefficient)	0.063	0.941
2.	TPSA (Polar surface area)	61.836	77.755
3.	n atoms (Number of non hydrogen atoms)	14.0	13.0
4.	MW (Molecular weight)	194.194	180.159
5.	n ON Number of hydrogen-bond acceptors (O and N atoms)	6	4
6.	n OHNH Number of hydrogen-bond donors (OH and NH groups)	0	3
7.	n violations (Number of rule of 5 violations)	0	0
8.	n rotb (Number of rotatable bonds)	0	2
9.	Volume (Molecular volume)	167.63	154.497

Table 2: Hex 6.0 docking score of proteins with caffeine

Protein name	E min	E max	E total
P53	-164.69	-120.64	-224.93
Bcl-2	-116108.93	-84888.53	-116108.93
Bax	-167.94	-104.85	-167.94
Caspase-9	-158.65	-103.86	-158.65

Table 3: Hex 6.0 docking score of proteins with caffeic acid

Protein name	E min	E max	E total
P53	-187.90	-115.10	-187.90
Bcl-2	-177.25	-177.84	-177.25
Bax	-176.99	-111.37	-177.0
Caspase-9	-160.50	-106.86	-160.50

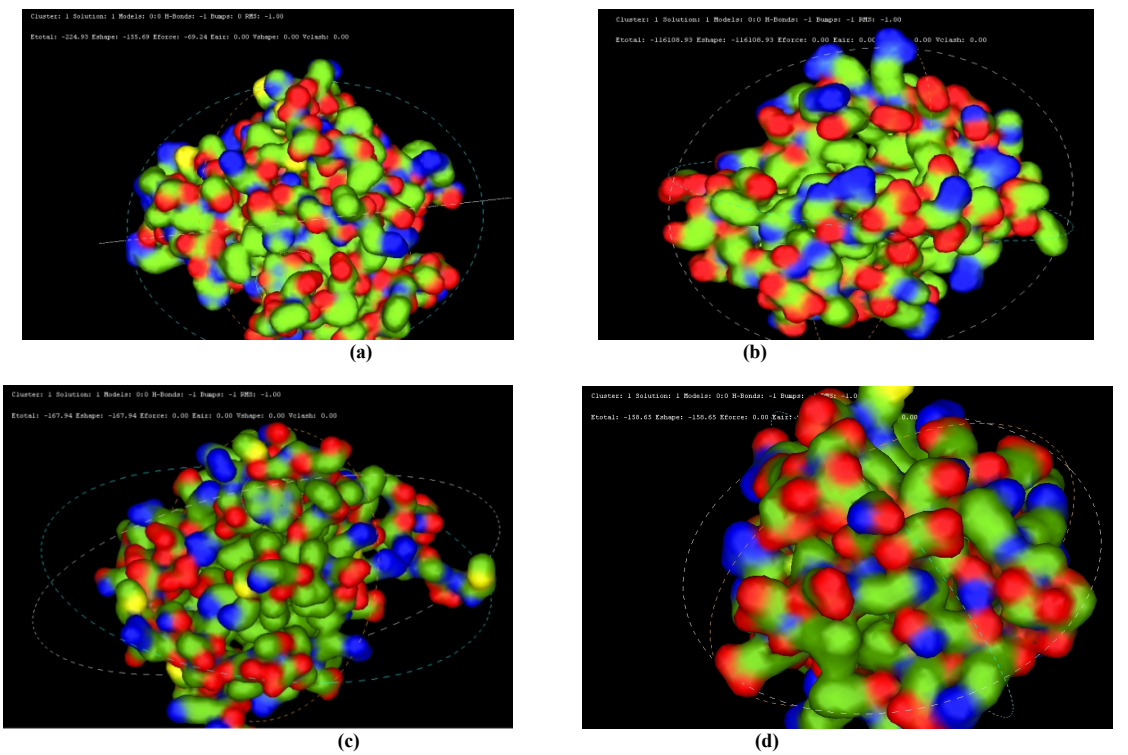

Figure 1: Docking struture of caffeine with (a) mutant P53, (b) Bcl-2,(c) Bax and (d) caspase-9

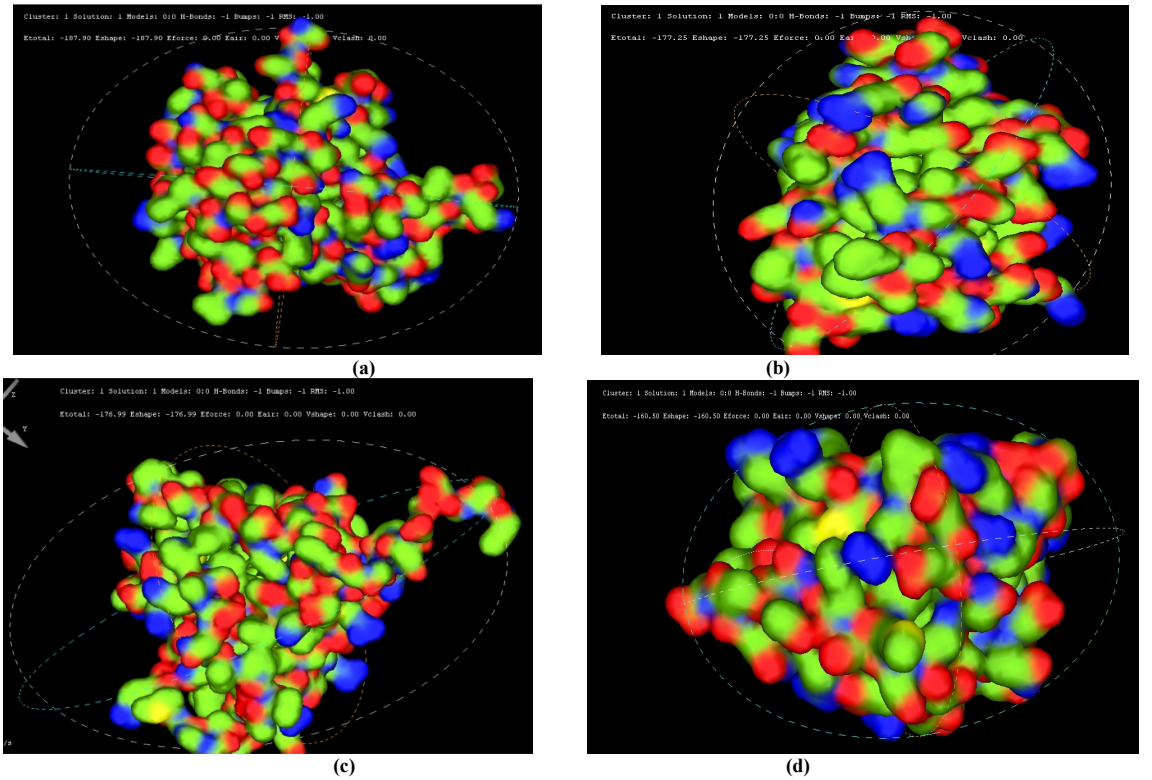

Figure 2: Docking struture of caffeic acid with (a) mutant P53, (b) Bcl-2,(c) Bax and (d) caspase9

RESULTS AND DISCUSSION

Structure-activity relationship, drug likeness, ADME/TOX properties of caffeine, caffeic acid has been analyzed by molinspiration tool. Synthetic and natural compounds using as drug against diseases need to under the rules and conditions, compounds were further evaluated for compliance with Lipinski's 'rule-of-five'. According to these rules molecular pharmacokinetic properties of a compound, that makes it potentially applicable as an oral drug. Most drug-like molecules have following: (i) log P < 5, (ii) Molecular weight < 500 Daltons, (iii) Less than 10 hydrogen bond acceptors, (iv) Less than 5 hydrogen bond donors. Molecules violating more than one of these rules may have problems with bioavailability[10]. Frequently the topological polar surface area (TPSA), the molecular volume, lipophilicity and solubility, widely acknowledged as an important element determining transport of drugs across membranes. Caffeine and caffeic acid having better drug-likeness properties and ADME properties and these compound pharmacokinetics properties not violating Lipinski rule (Table 1). Molecular Docking assessment using Hex 6.0, calculate protein ligand docking, assuming the ligand is rigid, and it Spherical Polar Fourier (SPF) correlations to accelerate the calculations, and it is still few docking programs that have built-in graphics to view the results[11,12] (Figure 1 and 2). The Selected proteins 3D structures were obtained by homology modeling using SWISS-MODEL server. Hex results showing caffeine, caffeic acid have better affinity with homology modeled selected apoptosis related protein such as mutant p53, Bcl-2, Bax and caspase-9. There are total four protein receptors, that all are showing efficient docked score. (Table 2 and 3) Caffeine docked with anti apoptotic Bcl-2 protein showing docking score of Etotal-116108.93. This is considering as a highest score in ligand interactions. Thereby caffeine, caffeic acid effectively inhibits/activate the tumor suppressor, anti-apoptotic protein and apoptosis effectors. These two could be lead molecule and having therapeutic efficacy of oral cancer.

CONCLUSION

Drug design, protein homology modeling, and docking studies are now promising tool towards the drug development. In the present study, evidence that caffeine, caffeic acid showing drug likeness, and ADME scores is no violation Lipink's rule of five. Hex 6.0 docking results showing good protein-ligand interacting scores with mutant p53, Bcl-2, Bax and caspase-9. Drug designing and docking of the drugs with the targeted protein provides good information of the mechanism in the development of a particular drug against the disease and cancer. The study of the comparative docking score helps to explain positive correlation between the docked ligand and receptor by perfect score. Hence, we conclude that these drugs might be having anticancer activity and further experimental studies need to confirm the apoptosis related protein activation in the oral cancer cells.

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