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Research Article

Role of 4-O Galloylchlorogenic Acid in Lung Cancer- An Insilico Approach

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ABSTRACT

Cancer is a major disease with millions of patients diagnosed each year with high mortality around the world. Various studies are still going on to study the further mechanisms and pathways of the cancer cell proliferation. Fucosylation is one of the most important oligosaccharide modifications involved in cancer and inflammation. In cancer development increased core fucosylation by FUT8 play an important role in cell proliferation. Down regulation of FUT8 expression may help cure lung cancer. Therefore the computational study based on the down regulation mechanism of FUT8 was mechanised. Sapota fruit extract, containing 4-Ogalloylchlorogenic acid was used as the inhibitor against FUT-8 as target and docking was performed using in-silico tool, Accelrys Discovery Studio. There were several conformations of the docked result, and conformation 1 showed 80% dock score between the ligand and the target. Further the amino acids of the inhibitor involved in docking were studied using another tool, Ligplot. Thus, in-silico analysis based on drug designing parameters shows that the fruit extract can be studied further using in-vitro techniques to know its pharmacokinetics.

Keywords: Fucosylation, in-silico, anti-inflammatory, docking, cancer.

INTRODUCTION

One of the most frequently diagnosed diseases leading to death is cancer[1]. The search for alternative methods of treatment for various diseases is on the rise due to the side effects of drugs used. On this platform, drugs from herbal plants are proving to be the right choice from the ancestral days, in India. A medicinal herb is a plant (or a plant part) used for therapeutic properties[2]. Medicinal plants serve as reservoirs of naturally available dugs which are pharmacologically active[3, 4]. It has already been established that chemopreventive drugs derived from natural products possess appreciably good benefit in the disease process, whereas the toxicity level is very low[5]. Plant-based diet, especially fruits and vegetables contain substantial quantities of molecules that have chemopreventive potential to fight against cancer development. Such compounds include vitamins, trace elements and a variety of other molecules with antioxidant and anti-inflammatory properties. Carotenoids, flavanoids, polyphenols, isoflavones, catechins, and several other components that are found in leafy and green vegetables are molecules that are known to reduce the risk from several forms of human cancers[6].

Lung cancer is the leading cause of cancer death among both men and women. The study by The Indian Council of Medical Research (ICMR) in 2016 have shown that person suffering from lung cancer is estimated to be 1.14 lakh (83,000 in males and 31,000 in females) and projected 1.4 lakh new cases in 2020[7]. Herbal medicine is the most commonly used group of treatment among complementary and alternative medicines. The oldest used system of medicine in the world is Herbal treatment with more than 2000 years history[8]. Herbs perform through numerous mechanisms to shield the body in the domain of cancer prevention. Dietary substances from plants have proved to be suitable candidates to treat various types of cancer[9,10]. Thus it can be understood that the risk of cancer can be repressed by eating more fruits, vegetables and other plant products[11,12]. One such fruit is Sapodilla plum commonly known as sapota.

Sapodilla plum (Achras sapota or Manilkara zapota) is a tropical evergreen fruit tree belonging to the family of sapotaceae used in traditional system of Indian medicine for its anti-inflammatory, antioxidant, antimicrobial, analgesic and spermicidal properties[11]. From ripe

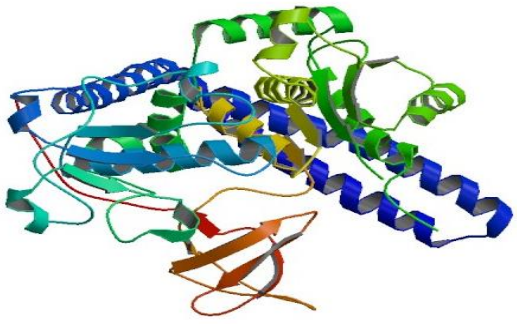

Figure 1: Structure of the enzyme Fucosyltransferase-8.

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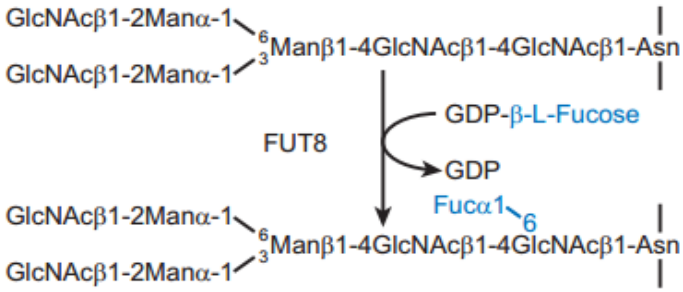

Figure 2: Catalysis transfer of Fucose residue from GDP fructose.

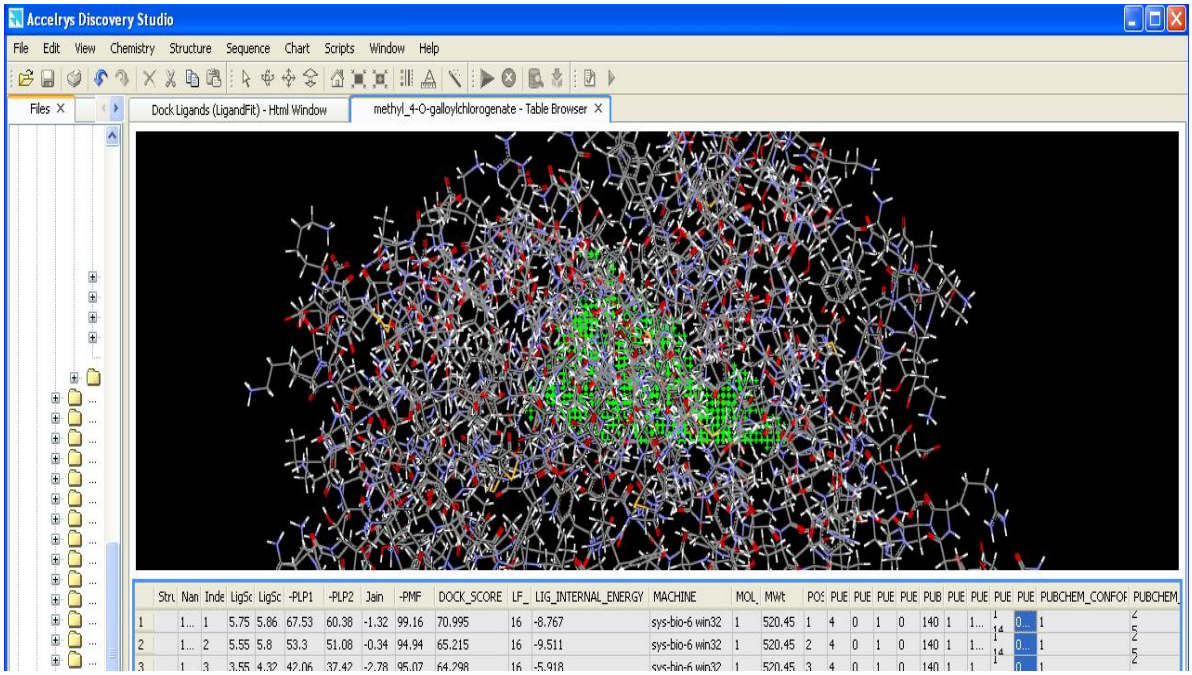

Figure 3: View of the protein in Discovery Studio.

Conformation S.No.	Ligand Score	Internal Energy	Dock Score
1.	5.75	-8.767	70.995
2.	5.55	-9.511	65.215
3.	3.55	-5.918	64.298
4.	5.35	-6.565	63.343
5.	5.35	-4.214	63.034
6.	3.81	-7.293	62.158
7.	4.54	-5.219	61.719
8.	4.85	-6.96	61.463
9.	5.81	-0.049	61.438
10.	4.13	-6.007	61.161

Table 1: Docking Parameters.

sapodilla fruits phenolics, carotenoids, ascorbic acid and chemical constituents such as flavonoids, polyphenols, dihydromyrecetin, quercitin, myricitrin, catechin, epicatechin, gallocatechin and gallic acid have been isolated[13-15]. One such phenolic antioxidants such as methyl 4-O-galloylchlorogenate and 4-O-galloylchlorogenic acid is found to cytotoxic to colon cancer cells[16].

MATERIALS AND METHODS

Identification of the ligand

From literature evidences, it can be seen that the components of sapota, viz., methyl 4-*O*-galloylchlorogenate and 4-*O*-galloylchlorogenic acid, has a cytotoxic property against colon cancer[16]. These were taken as ligands and their potential to inhibit cancer has been analysed.

Structure of the ligands and target

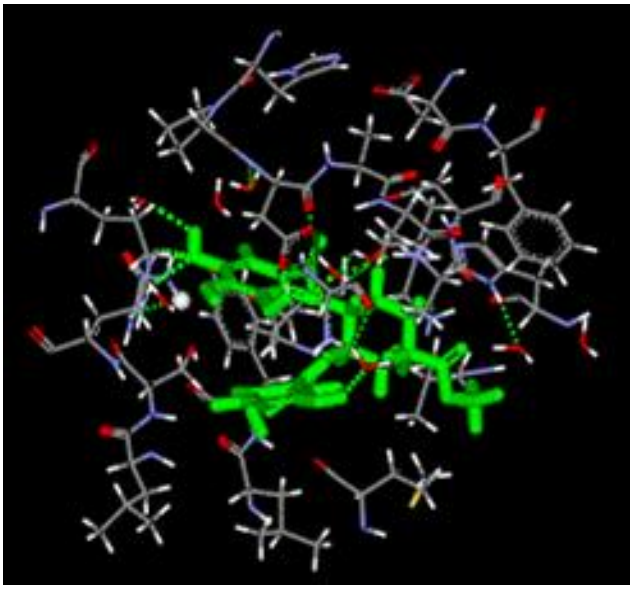

Figure 4: Docked Structure of target protein with ligand.

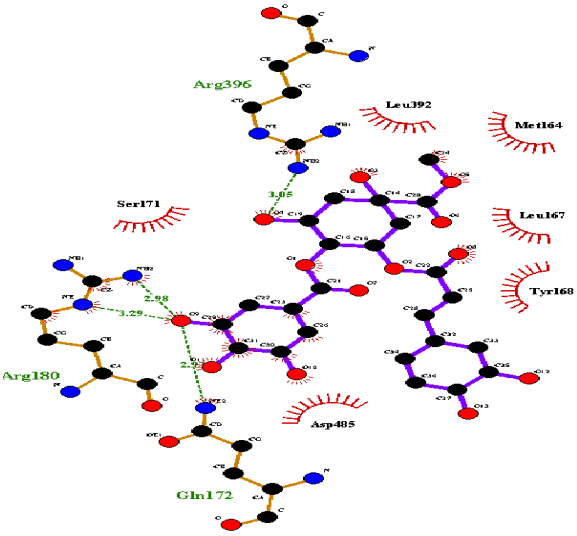

Figure 5: Ligplot analysis.

Following tools/databases were used for analysing the drug interaction(in sequence of use)-

- Protein Data Bank
- Rampage
- Pubchem
- Accelrys Discovery Studio 4.0
- Ligplot

The 3D structure of the ligand was taken from the PUBCHEM database. Lung cancer is the site selected for insilico analysis. The structure of α-1,6fucosyltransferase 8 (FUT8) was retrieved (fig1) using the PDB database of protein structures.

Docking analysis

Docking between the target protein (FUT8) and the ligand (4-*O*-galloylchlorogenic acid) was done using the Accelrys Dicovery Studio 2.1. Various binding sites and ligand conformations were tested and the best was selected based on Stability co-efficient and internal energies. Finally, the properties of the non-bonded interactions, ligplot analysis was performed using Ligplot+ was studied.

RESULTS AND DISCUSSION

Different components of the Sapota plant such as saponins and triterpenoids have been used in folk medicine and are known to exhibit anti-inflammatory, antioxidant, antimicrobial, analgesic and spermicidal activities[17-18]. Fucosyltransferase-8 (FUT8) is the enzyme whose up regulation results in proliferation of lung cancer cells .FUT8 is a typical type II membrane protein and is localised in golgi apparatus. Human FUT8 is located on chromosome 14q 23.3(20). FUT8 is widely expressed in human tissues at relatively high levels in the brain, LUNGS, stomach, small intestine and jejunum. Hence inhibiting the activity of this enzyme will reduce the growth of cancer cells.

FUT8 catalyses transfer of fucose residue from GDP fucose to the reducing terminal GlcNAc of Asn linked oligosaccharide via α-1,6 linkage, thus FUT8 also known to be α-1,6 FUT8 (Fig.2). The resulting fucosyl residue is referred to core fucose. Thus, over- expression and impaired function of FUT8 results in lung destructive phenotypes(cancer)[19].

Of the two ligand methyl 4-*O*-galloylchlorogenate (Fig.2) and 4-*O*-galloylchlorogenic acid, latter was further used for docking since it nearly favored the Lipnsky's Rule of Five. This ligand was used to dock with the target protein (FUT8).

Docking between the target protein (FUT8) and the ligand (4-*O*-galloylchlorogenic acid) was done using the Accelrys Discovery Studio 2.0. Various binding sites and ligand conformations were tested and the best was selected based on stability co-efficient and internal energies (Figure 3).

A resulting structure was obtained after the docking was performed. There were 15 binding sites found in the target protein (FUT8), where the ligand could bind. Out of the 15 binding sites, site 1 was selected based on the number of hydrogen bonds. The ligand to be bound to the target protein occurred in ten different conformations. The first one with highest dock score was selected and then the final docked structure was obtained. The following table.1 shows the different docking parameters to study the conformational properties.

With the above mentioned parameters, the conformation 1 was selected for docking as it had the highest dock score complementary to the lowest internal energy. Thus, the following figure 4 shows the docking of The non bonded interactions such as hydrogen bonds, α-1,6 Van der Waal forces, dipole interactions were studied further by doing a ligplot using a tool known as LIGPLOT+. This tool helps us to find the ligand interactions too. The structure obtained after the ligplot analysis is given below:

FUT8 globally modifies surface antigens, receptors,and adhesion molecules and is involved in the regulation of dozens of genes associated with malignancy. The interaction of (4-*O*-galloylchlorogenic acid) with Fucosyltransferase-8 (FUT8) inhibits core fucosylation

thereby reducing the ligand binding affinity of TGF-β1 receptor, EGF receptor which are responsible for downstream signaling. Moreover, it weakens cell–cell adhesion of E-cadherin and integrin α3β1 which plays an important role in cell proliferation and metastasis in cancer cell[20]. It has recently been reported that the deletion of the core fucose from the IgG1 molecule enhances antibody-dependent cellular cytotoxicity activity by up to 50–100 fold[21,22]. Thus down-regulation of Fucosyltransferase-8 inhibits cancer cell growth.

CONCLUSIONS

Thus, the conclusion was made that, by the interaction of the ligand(4-*O*-galloylchlorogenic acid) with the target protein(FUT8) enzyme, there is a possibility of down regulation of the enzyme FUT8 which may inhibit the cancer cell growth, thereby inducing apoptosis. Importantly, a previous study with Sapota stem bark extracts was also consistent with our observations[23, 24].

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