A Molecular Docking study to find Natural Inhibitor Against FAT10 Protein for curing Hepatic Carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC, also called malignant hepatoma) is the most common type of liver cancer caused by several factors and one of the them is the up regulation of FAT10 gene. The FAT10 gene is involved in cell-cycle regulation and modulator of tumor genesis therefore FAT10 protein targeted for our molecular docking study to find plant origin anti-hepatic carcinoma compounds. Docking analysis revealed that the plant compound Artonin E from the bark of Artocarpus gomezianus Wall. ex Tréc. (Moraceae) found close affinity for FAT10 protein as like chemical liver cancer drug Doxorubicin. Therefore, our research work concludes that plant origin compounds can act a potential inhibitor for FAT10 protein in order to regulate hepatic carcinoma.

Keywords:
Hepatocellular Carcinoma
FAT10 protein
Docking
Cell Cycle regulation

INTRODUCTION

Tumor genesis causes by deregulated cell-cycle control or apoptosis. The ubiquitin and its related families of proteins through target proteins modification disturb cellular processes including cell-cycle regulation [1] as well as cell death/ apoptosis [2] and responsible for many cancer. One of them is Hepatocellular carcinoma (HCC, also called malignant hepatoma) and is the most common type of liver cancer. Liver cancer is the fifth most common cancer in men and the seventh in women [3]. Most cases of HCC are secondary to either a viral hepatitis infection (hepatitis B or C) or cirrhosis (alcoholism being the most common cause of liver cirrhosis) [4, 5]. Genetically, FAT10 gene not previously related with HCC or other type of cancers is consistently up regulated in the tumors of approximately 90% of HCC patients screened [6, 7]. FAT10 is localized to the nucleus of HCC cells. The FAT10 gene is involved in cell-cycle regulation and modulator of tumor genesis [8, 9], and this
report represents the first demonstration of the up regulation of \textit{FAT10} gene over expression is related to gastrointestinal and gynecological tumors [10]. Gene targets of TNF-α, FAT10 or di-ubiquitin (UBD), all synergistically inducible by TNF-α and IFN-γ (interferon gamma) (TI) as well as retinoid [11, 12].

Plants and plant compounds are reported with anticancer effects [13]. “Terpenoids have been found to be useful in the prevention and therapy of several diseases, including cancer, and also to have antimicrobial, antifungal, antiparasitic, antiviral, antiallergenetic, antispasmodic, anti hyperglycemic, anti-inflammatory, and immuno-modulatory properties.” [14]. Several Plant origin compounds have been investigated to design drugs against diseases causing organisms or pathogenic proteins such as H1N1 virus [15], NADP oxidoreductase [16], DNA glycosylase [17], Mycobacterium tuberculosis [18] and Nudix Enzyme [19]. Also reports are available where plant compounds can suppress the growth of many types of cancer cells and have chemo preventive and therapeutic effects against liver cancer, colon, breast, prostate and skin cancer [20]. Here in our work, we are focusing on application of computational docking method to find plant origin anti-tumor inhibitor for \textit{FAT10} protein.

**MATERIALS AND METHOD**

**Protein file**
The X-ray crystalline structure of \textit{FAT10} structure was obtained from RCSB protein data bank (PDB Code: 2MBE). The whole structure of the \textit{FAT10} protein was targeted for our molecular docking study.

**Compounds library**
Information of different anti-tumor plant compounds were collected from the literatures. Thanks to the Ayurvedic science and reports available for plant derived anti-tumor compounds. Total 29 anti-tumor plant compounds were listed from the literatures and their SMILES strings were obtained from PUBCHEM database. CORINA demo server (http://www.molecular-networks.com/online_demos/corina_demo) was employed in order to convert the SMILES strings of the compounds into 3D structures. Different anti-hepatic carcinoma drugs information were also obtained from Drug bank database (www.drugbank.ca) and their 3D structures were downloaded.

**Automatic Docking**
The computational molecular docking method was employed for screening of anti-tumor plant compounds and the anti-hepatic carcinoma drugs against the structure of FAT10 protein. The molecule docking was performed by iGemdockv2.1 software. We selected the Drug Screening platform of iGemdock for doing our computational docking. The following parameters were selected for docking such as Population size: 200, Number of generations: 70 and Number of solutions: 3. The anti-tumor compounds were sorted at the end of docking process based on their interaction energies and fitness values produced by the docking via iGemdock software. The most stable conformation of the plant origin anti-tumor compound was selected based on the lowest fitness value. Furthermore, the compound binding was analyzed at the active site of the FAT10 protein by discovery studio software.

**Z score analysis**

Statistical test such as Z score was performed for the interaction energies produced by iGemdock. The Z score determines the uniqueness and confidence in the docking result. The measurement of Z score demonstrates the affinity between anti-tumor compounds and FAT10 protein. It shows that the affinity produced by the best compound (with lowest interaction energy) for FAT10 protein is unlikely to produce by other compounds in random population. Later the best compound was selected with based on more negative Z score of interaction energy and P value less than < 0.05 (95% confidence interval).

\[
Z = \frac{(x-\mu)}{\sigma}
\]

**RESULTS**

Total 29 plant anti-tumor compounds were screened against the structure of FAT10 protein via iGemdock. We found that Artonin E produced greater affinity for the FAT10 protein with the first rank. It binds with the FAT10 protein with interaction energy (fitness value) of -104.868 kcal/mole. Fig. 1 shows distribution of interaction energies (fitness values) produced after docking of plant anti-tumor compounds against FAT10 protein. It shows that interaction energy of Artonin E is unique and not able to produce by other compounds. Second rank is obtained by Abyssinone with interaction energy of -95.814 kcal/mole. Z score analysis reveals that Artonin E produces lowest value of Z score of -1.591 which determines the uniqueness and
confidence in the affinity of Artonin E for FAT10 protein (Table 1). It shows that the affinity produced by the Artonin E (with lowest interaction energy and Z score) for FAT10 protein is unlikely to produce by other compounds in random population.

Doxorubicin produces the Z score of -1.755. The docking results indicate that plant anti-tumor compound Artonin E has affinity comparable to the chemical drug Doxorubicin for FAT10 protein.

**Binding site Residues**

On the other hand, screening of chemical anti-tumor drugs shows that the only drug Doxorubicin shows good affinity against the FAT10 protein with interaction energy of -107.80 kcal/mole. This affinity is slightly higher than the plant compound Artonin E where interaction energy is -104.868 kcal/mole. Also the Z score analysis reveals the confidence on the docking results where
Table 1: Interaction Energies and Z score of Top Compounds.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compounds</th>
<th>Interaction Energy (-kcal/mole)</th>
<th>Fitness value</th>
<th>Z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Artonin E</td>
<td>-104.868</td>
<td></td>
<td>-1.591</td>
</tr>
<tr>
<td>2</td>
<td>Abyssinone</td>
<td>-95.814</td>
<td></td>
<td>-1.085</td>
</tr>
<tr>
<td>3</td>
<td>Artonol</td>
<td>-94.652</td>
<td></td>
<td>-1.020</td>
</tr>
<tr>
<td>4</td>
<td>Sorafenib</td>
<td>-80.25</td>
<td></td>
<td>-0.215</td>
</tr>
<tr>
<td>5</td>
<td>Doxorubicin</td>
<td>-107.80</td>
<td></td>
<td>-1.755</td>
</tr>
<tr>
<td>6</td>
<td>Cisplatin</td>
<td>-46.30</td>
<td></td>
<td>1.682</td>
</tr>
</tbody>
</table>

Binding site analysis shows that Doxorubicin makes hydrogen bond interactions with Asp 16, Arg54, Ser57, Ile61 and Lys63. In addition, Artonin E makes hydrogen bond interactions with Asn 18, Arg53 and Lys 25.

**DISCUSSION**

We determine the effectiveness of the computational molecular docking method to find alternative natural origin medicine for treating the hepatic carcinoma. The automated docking software iGemdock is able to detect that Artonin E shows good affinity for FAT10 protein, close to the chemical drug Doxorubicin. Artonin E (AE) is a 3-prenylflavone compound extracted from the bark of *Artocarpus gomezianus* Wall. ex Tréc. (Moraceae) (Fig. 3). Other species of genus *Artocarpus* such as *A. scortechinii*, *A. rotunda*, *A. rigida* and *A. altili* also have Artonin E. It is also reported that Artonin E has very potential pharmacological properties [21], antimicrobial [22], antimalarial, antituberculosis [23] and cytotoxicity [22, 23].
CONCLUSION
Our molecular docking work concludes that Artonin E has compatible affinity for the FAT10 protein as shown by chemical anti-hepatic carcinoma drug Doxorubicin. Our computational docking work reveals that plant anti-tumor compound Artonin E can be useful to treat Liver cancer. As plant origin of Artonin E, therefore, it is easily available and produce no side effect. Our research work may help the medical biologist to find potential drugs from natural compounds against the hepatic carcinoma.

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