Camptothecins And Their Novel Anticancer Properties Evaluated By Using Pass Method

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ABSTRACTS

Chemotherapy is one of the approaches applied for cancer treatment. Most of the drugs used today in chemotherapy have natural origins and were first discovered in plants, fruits and microorganisms. Camptothecins are natural anticancer agents initially extracted from bark and leaves of Camptotheca acuminate trees. This study examined the anticancer bioactivity as well as Drug-like properties of these compounds. Accordingly, the structures of the following compounds were drawn with ChemAxon and evaluated with PASS software for about 1500 possible activities mechanisms and targets: Camptothecin (CPT), Irinotecan, Topotecan, 9-Nitrocamptothecin and 10-Hydroxycamptothecine. In addition, further intergroup analyzes were accomplished. Results represented that all compounds have strong Antineoplastic Alkaloid, Topoisomerase I inhibitory and DNA intercalator activities with higher than 0.6 thresholds. This is interesting that they have high drug-likeliness simultaneously. So all camptothecins were categorized in three main groups based on their strong exhibited activity. Consequently, Camptothecin (CPT), 10-Hydroxycamptothecin (10-HCPT), with 0.87 mean activities were the strongest anticancer agents among the other camptothecins.

Introduction

Cancer is a kind of disease characterized by uncontrolled cell growth and spread of the abnormal cells, and is caused by acquired genetic alternations of somatic cells. Currently, there are several approaches used for cancer treatment such as: Surgery, Chemotherapy, Immunotherapy (monoclonal - antibody), Radiotherapy and Gene-therapy. Most of the drugs being used today in chemotherapy have natural origins and were first discovered in plants, fruits or microorganisms. Therefore, Plants are important source of anticancer molecules which target different pathways of cancer progression. Camptotheca (Happy tree) is a genus of medium-sized deciduous mainly found in southern of China and Tibet. There are two species of Camptotheca (i.e. Camptotheca acuminata and Camptotheca lowreyana). Camptotheca acuminata species is rich of new antineoplastics agents, for instance: Camptothecin (CPT), Irinotecan, Topotecan, 9-Nitrocamptothecin and 10-Hydroxycamptothecine. Camptothecin is the first compound in this class extracted from bark and leaves of Camptotheca acuminate tree species. Irinotecan and Topotecan are semisynthetic analogue of natural alkaloid Camptothecin, and currently are the most widely used camptothecin analogs in clinical experiments that targets topoisomerase I enzyme. 9-Nitrocamptothecin and Hydroxycamptothecine (10-HCPT) are analogs of the natural Camptothecin family.

Previous investigations of scientists in the world have revealed that Camptothecin (CPT), 10-Hydroxycamptothecin (10-HCPT), 9-Nitrocamptothecin inhibit topoisomerase I enzyme in order to have anticancer properties. Topoisomerase I is a nuclear enzyme that breaks unwinds the positive super coils of DNA. Subsequently, the break is sealed and the linkage number is changed by 1, and permit essential cellular process (i.e DNA replication, recombination, repair and transcription) to occur. The camptothecins definitely bind to topoisomerase I and stabilize DNA-topoisomerase I cleavable complex. Currently this study is focused on another target of Camptothecin (CPT), 10-Hydroxycamptothecin (10-HCPT), 9-Nitrocamptothecin molecules. Moreover, Bioinformatics tools such as PASS are applied to predict bioactivities and properties of these anticancer agents. We believe...
that it can be as an approach in order to recognize the new mechanisms of action of anticancer compounds.

**Material and Method**

**Data:**

A practical database is the main step in bioinformatics projects. Collection of data from Pubmed database were accomplished with general keyword “anticancer”. Most data were gathered from 2010 papers; therefore, anticancer molecules were extracted from this papers, and defined their targets in apoptotic pathway. In this case molecules were classified based on their origins, as a result we had 7 groups of anticancer molecule such as molecules in Drug Bank, plants, fruits, microorganisms, semisynthetic agents, synthetic agents and finally ungrouped anticancer agents which their origins were unknown.

**Structure:**

Structural formula of these molecules were investigated from Chemspider, Pubchem and Wikipedia, respectively, and the original molecular structure of all compounds were found, their skeletal structures drawn with Chemschetch, Chemaxon, version 5.4 software in order to reach 3D structures of molecules within MDL SD file, the same software is used with molecular mechanics algorithm for structural optimization. ChemAxon is a leader in providing Java based chemical software development platform for biotechnology and pharmaceutical industries. Protein Data Bank (PDB), Tripos MOL2, MDL MOL and SD file formats were saved, too (figure 1).

**Docking:**

All molecules were predicted for their possible bioactivities with PASS, V.poroikov et al, version 1.917, software. PASS (Prediction of Activity Spectra for Substance) is a simple computational tool that can predict more than 1500 pharmacological effects, molecular mechanisms of action, and toxicities on basis of structural descriptors of compounds. The top molecules with more than 0.6 score anticancer activity were selected and categorized on basis of their targets.

**Results and Discussions**

Screening is basis of this project which was applied at each step. About 292 molecules were gathered from searched papers, and PubChem
Chemspider database were looked for finding structural formulas of these screened molecules. Accordingly, nearly 242 molecules had available formula structure, were evaluated with PASS in order to predict compounds with high anticancer activity. All Camptothecins exhibited anticancer activities more than 0.6 score and were screened. Figure 2 exhibits platform of PASS software with anticancer analysis of Camptothecins.

![Image]

**Fig. 2:** Platform and analysis of a molecule for its anticancer activity with PASS software

Camptothecins with their docking score of their antineoplastic, topoisomerase I inhibitory, DNA intercatator activity are shown in Tables 1, 2, and 3. Also drug-likeesses were derived by PASS software in order to estimate cytotoxicity of camptothecins compounds. Figures 3, 4, and 5 represented the docking score of Camptothecins in details.

**Figure 3** depicts antineoplastic alkaloid activities of Camptothecins and it is mentioned that they have a strong antineoplastic alkaloid activities. However, no significant difference was observed among their scores.

**Table 1.** Pass prediction of antineoplastic property

<table>
<thead>
<tr>
<th>Molecules</th>
<th>Pass activity (antineoplastic)</th>
<th>Pass inactivity (antineoplastic)</th>
<th>Drug likeness</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Camptothecin</td>
<td>0.712</td>
<td>0.002</td>
<td>0.990</td>
</tr>
<tr>
<td>B Irinotecan</td>
<td>0.807</td>
<td>0.002</td>
<td>0.992</td>
</tr>
<tr>
<td>C Topotecan</td>
<td>0.615</td>
<td>0.002</td>
<td>0.989</td>
</tr>
<tr>
<td>D 10-Hydroxycamptothecin</td>
<td>0.720</td>
<td>0.002</td>
<td>0.991</td>
</tr>
<tr>
<td>E 9-Nitrocamptothecin</td>
<td>0.619</td>
<td>0.002</td>
<td>0.950</td>
</tr>
</tbody>
</table>

![Antineoplastic alkaloid activity diagram]

**Fig. 3:** Antineoplastic alkaloid activity of Camptothecins.
As can be seen from Figure 4, all of the Camptothecins are potent topoisomerase I inhibitors and all of them show this property more 0.781. Moreover, the frequency of topoisomerase inhibitory isn’t so different among them.

Table 2. PASS prediction of topoisomerase I inhibitor activity

<table>
<thead>
<tr>
<th>Molecules</th>
<th>Pass activity (Topoisomerase I inhibitory)</th>
<th>Pass inactivity (Topoisomerase I inhibitory)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A  Camptothecin</td>
<td>0.952</td>
<td>0.001</td>
</tr>
<tr>
<td>B  Irinotecan</td>
<td>0.781</td>
<td>0.002</td>
</tr>
<tr>
<td>C  Topotecan</td>
<td>0.846</td>
<td>0.002</td>
</tr>
<tr>
<td>D  10-Hydroxycamptothecin</td>
<td>0.948</td>
<td>0.001</td>
</tr>
<tr>
<td>E  9-Nitrocamptothecin</td>
<td>0.858</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Fig. 4: Topoisomerase I inhibitor activity of Camptothecins.

According to Figure 5, the most potent property that Camptothecins have showed, is DNA intercalator activity.

Table 3. PASS prediction of DNA intercalator activity

<table>
<thead>
<tr>
<th>Molecules</th>
<th>Pass activity (DNA intercalator activity)</th>
<th>Pass inactivity (DNA intercalator activity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A  Camptothecin</td>
<td>0.972</td>
<td>0.001</td>
</tr>
<tr>
<td>B  Irinotecan</td>
<td>0.816</td>
<td>0.002</td>
</tr>
<tr>
<td>C  Topotecan</td>
<td>0.874</td>
<td>0.002</td>
</tr>
<tr>
<td>D  10-Hydroxycamptothecin</td>
<td>0.961</td>
<td>0.001</td>
</tr>
<tr>
<td>E  9-Nitrocamptothecin</td>
<td>0.885</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Fig. 5: DNA intercalator activity of Camptothecins.
Discussion:

Previous papers demonstrated that Camptothecins have anticancer activities, scientists mentioned antineoplastic and topoisomerase I inhibitor activity of Camptothecins (12). It is suggested that Camptothecin interact with the enzyme-DNA complex through hydrogen bonds. On the other hand, Topotecan acts through forming a stable covalent complex with DNA/TOP-1 complex, in order to breaks in DNA strand. This results in apoptosis and cell death. In addition, Camptothecins have a dose limiting side effects, because of this, they are applied in many cancers for instance (Reference 21). 10-Hydroxy camptothecin and Camptothecin are used in breast cancer and targets MCF-7 cells, also 10-Hydroxy camptothecin (Reference 6) is applied in human colon cancer and arrested Colo 205 cells in G2 phase of cell cycle and induces apoptosis through caspase-3 dependent pathway. So, analysis of Camptothecins with PASS could predict more properties of these molecules and highlighted their toxicities. As a result, three main characteristics of molecules were antineoplastic alkaloid activities, topoisomerase I inhibitory and DNA intercalator potency. Among Camptothecins family, Irinotecan showed the highest antineoplastic alkaloid activity with 0.807 score. However, Topotecan had the lowest antineoplastic alkaloid activity with 0.615 score, but no significant difference was observed among their scores. Camptothecins are potent topoisomerase I inhibitors and all of them show this property more 0.781 score. Although, Camptothecin exhibited the highest topoisomerase I inhibitor activity with 0.952, 10-Hydroxy camptothecin also revealed high score of topoisomerase I inhibitor potency 0.948. The highest bioactivity that Camptothecins show is DNA intercalator activity as well as prediction scores revealed that Camptothecin with 0.972 was the most potent DNA intercalator inhibitor. Likewise, 10-Hydroxy camptothecin with 0.961 also was as a potent DNA intercalator agent too.

It is noteworthy that the mean score of each molecule was higher than 0.77 and it was indicated that all of them were potent anticancer agents that definitely were antineoplastics, topoisomerase I inhibitor and DNA intercalator agents. Interestingly, both of the Camptothecin and 10-Hydroxy camptothecin had the same mean score, and they were the most potent agents between the other Camptothecins. These compounds released Drug likenesses score were higher than 0.9. It means that they are as suitable drugs in chemotherapy. The detailed analysis of these compounds and their derivatives may improve our knowledge in finding new candidate anticancer drugs.

References