Evaluating New Targets of Natural Anticancer Molecules through Bioinformatics Tools

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Abstract

Plants-derive compounds play crucial role in development of several anti-cancer drugs and they target proteins having significant regulatory effects on tumor cell cycle progress. Bioinformatics and cancer research overlap in many different areas in order to solve some problems in the field of treatment. In this study, the target and drug likeness of natural anticancer molecules are predicted by PASS software. Consequently, some new mechanisms of anticancer molecules have been introduced. They include Pseudobaptigenin with 0.702 PASS thresholds which revealed protein tyrosine kinase inhibitory. In addition, Kabophenol A and Carasinol B with score 0.652 and 0.669 respectively exhibited topoisomerase I inhibitory effects. Moreover, Docetaxel, 7-xylosyl-10-deacetyl paclitaxel and Artemether by exhibiting the highest PASS score are the strongest anticancer agents in our research. It is noticeable all of studied agents exhibited high drug-likeness score and it means that they can be applied as drug.

Keywords: Natural anticancer molecule; Bioinformatics; PASS software; Cancer

Introduction

Cancer is disorder of cells growth. It starts when a normal cell begins to grow in an uncontrolled and invasive way. Cancer is thought to be caused through the interaction between genetic susceptibility and environmental toxins [1]. There are several ways which are applied for cancer treatment, for instance: Surgery, Chemo-therapy, Immuno-therapy (monoclonal antibody), Radiotherapy and Gene-therapy.

Chemotherapy is a kind of cancer treatment; it acts by destroying cells which are dividing rapidly. It means that it also has an effect on normal cells, such as: bone marrow, digestive tract, and hair follicles. Therefore, it results in side effects on patients who are exposed to chemotherapy. Most of the chemotherapeutic drugs target mitosis cell division in order to inhibit the hyperproliferation state of tumor cells and subsequently induce apoptosis. The majority of chemotherapeutic drugs can be clustered in alkylating- agents, antimetabolites, anthracyclines, plants alkaloids, topoisomerase inhibitors and other antitumor agents. The anticancer drugs can be subdivided in three main groups based on their mechanisms of action: (i) drugs that interfere with DNA synthesis, (ii) drugs that induce DNA damages, (iii) drugs that inhibit function of the mitotic spindle [2]. Plants are important source of anticancer agents and plant-derived compounds have played crucial role in development of several useful clinical anti-cancer drugs.

Bioinformatics is the mathematical, statistical and computing method that aims to solve biological problems. Bioinformatics can be applied in the field of medical sciences to consider the molecular pathways of diseases [3]. By developing sophisticated bioinformatics software’s such as PASS (Prediction of activity spectra for substances); it is now possible to predict some targets of anticancer molecules on the basis of structural formula of a substance accurately. This study focused on some natural anticancer molecules, including: Docetaxel, 7-xylosyl-10-deacetyl paclitaxel, Pseudobaptigenin, Kabophenol A, Carasinol B, 7β-hydroxyisosterol, Dehydrocostuslactone, and Artemether. By applying PASS software, we found targets of these natural molecules and classified them based on their targets in cancer pathway. We believe that it can be as an efficient approach for recognizing new mechanisms of anticancer compounds.

Materials and Methods

Data

A practical database is the main step in bioinformatics projects. Collection of data from Pubmed database was accomplished with general keyword “anticancer”. Most data were gathered from 2010 papers; therefore, known anticancer molecules and some information relevant to their targets in apoptotic pathway were extracted from these papers. In this case, molecules were classified based on their origins. As a result, there were 7 groups of anticancer molecule such as Drug Bank, plants, fruits, microorganisms, semi-synthetic, synthetic and finally ungrouped anticancer agents [4].

Structure

Structural formulas of these molecules were investigated from Chemspider, Pubcheme and Wikipedia, respectively in order to discover orginal molecular structure of all compounds. Then, their skeletal structures were drawn by Chemsetch, Chemaxon and version 5.4 software. ChemAxon is a leader in providing Java based chemical software development platform for biotechnology and pharmaceutical industries and is applied to reach 3D structure of molecules within MDL SD file, Protein Data Bank (PDB), Tripos MOL2 formats (Figure 1).

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 based on structural descriptors of compounds with over 80% accuracy. It also

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has capability to predict many types of activity for a new substance. PASS normally utilizes input data with molecular structure Protein Data Bank (PDB), Tripos MOL2, MDL MOL and SD file formats then represent the structural information about molecules under study. PASS prediction can be interpreted by Pa and Pi values. Pa and Pi values are as measures that determine activity and inactivity of compounds. Pa –the probabilities of being active and close to 1.000, Pi –the probabilities of being inactive close to 0.000; therefore, the Pa and Pi values vary from 0.000 to 1.000 and in general Pa+Pi<1.

PASS software works successfully on a PC running Vista, windows 7 and XP. In this study PASS version 1.917 was applied (Figure 2) and molecules with Pa more than 0.6 have been selected and categorized based on their targets in cancer pathway.

MNA (Multilevel Neighborhoods of Atom) descriptors are one the sections in PASS software that are utilized for assessing of chemical similarity based on 2D description of molecules and appropriate for use in QSAR (Figure 3). According to (Robustness provoke) MNA descriptor doesn’t specify the bond type and comprises hydrogen according to a valence and partial charge of atoms; thus, it is based on structure representation.

**Results**

Nearly 242 molecular structures were collected from PubChem, Chemspider database and Google search, these compounds were evaluated by PASS software in order to screen compounds with high anticancer activity and specify their targets during cancer pathway. Among these natural molecules, approximately 9 agents revealed anticancer activity with Pa more than 0.6 and they targeted specific proteins throughout cancer pathway. As it can be seen from table 1, *Docetaxel* and *7-xylosyl-10-deacetyl paclitaxel* are as Microtubule formation inhibitors, β-tubulin antagonists, antimitotic agents because they showed Pa>0.6. Thus, according to their high Pa scores these molecules are as promising anticancer agents. It can be seen form table 2 that mentioned agents target PTK, Topoisomerase I, MYC, DNA and protein efficiently and *Artemether* with Pa 0.8 are categorized as the most strong agent compare to other 6 molecules.

PASS software also has capability to estimate drug likeness of under study agents. Drug-likeness referred to specific score estimated from the molecular structure and indicated that specific molecule have some proportional properties which can be active biologically or might show therapeutic potential. Consequently, all 9 agents exhibited drug-likeness more than 0.9 and it means that they can be applied as drug.

**Discussion**

In this paper, a mathematical approach is discussed to evaluate anticancer activity of molecules based on Pa activity. PASS (Predication of Activity Spectra for Substances) software capable of anticipating more than 1500 pharmacological effect that can be efficiently applied to find new targets for some ligands to reveal new biological activity of various substances as natural molecules have less side effects compared to synthetic ones, we tried to discover new natural anticancer drugs which target specific cancer targets efficiently and develop the spectrum of efficient anticancer of molecules.

Microtubules are key components of cytoskeleton, and are formed from tubulin molecules. They have crucial role in development and maintenance of cell shape, in transport of vesicles, mitochondria and other components throughout cells, in cell movements, in cell signaling as well as in cell division and mitosis [5]. Microtubules are the target of variety of specific antimitotic drugs. Antimitotic drug exerts its effect by causing disorganized stabilization of microtubules in area away from the centriole or causing destabilization of mitotic spindle which...
is interfering with mitosis [2]. Docetaxel is semisynthetic analogue of Paclitaxel and they bind to microtubules with high affinity in order to stabilize microtubules and prevent from depolymerization. 7-xylosyl-10-deacetyl paclitaxel is isolated from Taxus Chinensis, which exhibits higher water solubility than Paclitaxel [6] demonstrated that 7-xylosyl-10-deacetyl paclitaxel induced mitotic cell cycle arrest and apoptosis.

It can be seen from table 1, both molecules have microtubule formation inhibitory, Docetaxel exhibited higher Pa score (0.986) compared to 7-xylosyl-10-deacetyl paclitaxel (0.757) and it means that Docetaxel can prevent from forming microtubules with more strength. In addition, they are as β-tubulin antagonists too and there isn’t apparent difference among their PASS thresholds, therefore, they reveal this property with the same strength. Moreover, Docetaxel and 7-xylosyl-10-deacetyl paclitaxel have strong anti-mitotic activity and their scores are 0.992 and 0.868 respectively. As a result, both molecules are promising anticancer agents which act through binding to microtubules and tubulins. According to their drug likeness score, they can behave as an efficient drug.

Protein Kinases are vital components of signal transduction pathways. They act through responding to the extracellular environment for regulating both cell growth and modification. Protein tyrosine kinases have enormous roles in cancer molecular pathogenesis, and they are as potential target for anticancer drugs currently [1]. There are two classes of protein tyrosine kinase inhibitors. One is bound to the ATP binding site and the other is bound to the substrate binding site of the enzyme. For instance, Pseudobaptigenin is an isolavone which can be isolated from Trifolium pretense [7] revealed that this agent has an antiproliferative effect, but no reference has been indicated to the principle target of Pseudobaptigenin in cancer pathway. Fortunately our results revealed that Pseudobaptigenin with 0.702 PASS score has high Protein Tyrosine Kinase inhibitor activity.

DNA topoisomerases are a class of enzymes involved in the regulation of DNA supercoiling during replication. Type I topoisomerases cut one strand of double-strand DNA, relax the two strands and then reanneal the strand [8]. Kabophenol A and Carasinol B are stilbene tetramers, which can be isolated from Caragana chamagune and Caragana sinic. It is demonstrated that Kabophenol A has effect on MCF-7 cells. While previous references didn’t mention to main target of Carasinol B and Kabophenol A in cancer pathway, we found that these two molecules, which have 0.669 and 0.652 score chronologically, have potent effects on Topoisomerase I. Therefore, they have anticancer property and exert their anticancer effects by inhibiting Top I enzyme.

Myc is a very strong Proto-oncogene which is expressed at elevated levels in different types of tumors. Myc is as a suitable target for development of novel cancer therapies and by designing drugs which inhibit tumor cell proliferation and/or increase apoptosis; we can extend the spectrum of anticancer agents. 7β-hydroxysitosterol is a type of sterol, is extracted from Selaginella Tamarriscina [9] revealed that this molecule exhibited potent cytotoxicity. Our results suggested that 7β-hydroxysitosterol by exhibiting 0.657 PASS threshold has strong Myc inhibitor activity.

Aromatase is an enzyme, which is a member of cytochrome p450 superfamily, it is located in the endoplasmic reticulum of the cell. The aromatase enzyme can be found in many tissues including gonads, brain as well as in tissue of endometriosis, uterine fibroids, breast cancer and endometrial cancer. Therefore, aromatase is as a critical target for cancers treatment. Aromatase inhibitors are class of drugs used in treatment of cancers; these agents block the synthesis of Estrogen in order to reduce the level of Estrogen. Consequently, the rate of cancer growth will be slowed. Dehydrocostuslactone is a sesquiterpene lactone extracted from Saussurea lappa and Aucklandia lappa. Dehydrocostuslactone induces cell cycle arrest at G2/M, causes cell cycle arrest via CDK1 down-regulation. According to our PASS results, this natural agent by exhibiting Pa 0.656 is an aromatase inhibitor agent and its high Drug-likeness score (0.995) related to the fact that it might possess functional groups or has physical properties which are consistent with most of known drugs [10].

DNA synthesis (DNA replication) refers to the process of copying each DNA strand into a new complementary strand. DNA replication inhibitors are commonly used as anticancer agents. Artemether is a methyl ether derivative of Artenisin is isolated from the leaves of Artemisia annua [11] demonstrated that the natural agent arrests cell cycle at G2. Fortunately this agent exhibited the highest Pa score (0.801) in compare to other agents and it means that Artemether is as a strong DNA synthesis inhibitor and can be as promising anticancer drug.

Protein synthesis is the process in which cells build proteins. A previous study showed that deregulation of protein synthesis is a major contributor in cancer initiation and metastatic progression. Acemannan is a D-isomer mucopolysaccharid in Aleo vera leaves [12]. This compound displayed chromatin condensation, DNA fragmentation and laddering characteristic of apoptosis. It is notice worthy that Acemannan with 0.613 Pass threshold has protein synthesis inhibitor properties and it acts by inhibiting protein synthesis.

### Conclusion

On basis of our study, it is mentioned molecules have strong anticancer characteristic and among all of them Docetaxel, 7-xylosyl-10-deacetyl paclitaxel and Artemether by exhibiting the highest PASS score are the most potent agents in our research. In addition, we found
fundamental target of *Pseudobaptigenin kobophenol A* and *Carasinal B* throughout cancer pathway in order to provide new insight of subsequent research into these agents because in vitro and in vivo experiments of these finding haven’t been applied until now. It is supposed that by applying these types of experiment new properties of these molecules will be appeared.

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