Journal of
Proteomics & Bioinformatics

Hashemi et al., J Proteomics Bioinform 2012, 5:2
DOI: 10.4172/jpb.1000212

Research Article Open Access

Evaluating New Targets of Natural Anticancer Molecules through Bioinformatics Tools

Mehrdad Hashemi*, Newshan Behrangi, Hojat Borna and Alireza Akbarzadeh

Department of Genetics, Islamic Azad University, Tehran Medical Branch, Tehran, Iran

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 notice worthy 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-hydroxysitosterol*, *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 Pub med 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 Chemschetch, 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

***Corresponding author:** Mehrdad Hashemi, Department of Genetics, Islamic Azad University, Tehran Medical Branch, Tehran, Iran, E-mail: mhashemi@iautmu.ac.ir

Received December 30, 2011; **Accepted** January 30, 2012; **Published** February 29, 2012

Citation: Hashemi M, Behrangi N, Borna H, Akbarzadeh A, et al. (2012) Evaluating New Targets of Natural Anticancer Molecules through Bioinformatics Tools. J Proteomics Bioinform 5: 050-053. doi:10.4172/jpb.1000212

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 are 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,

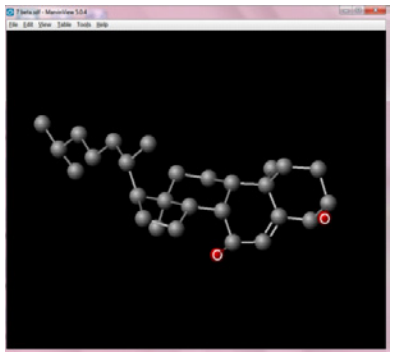

Figure 1: 3D structure of 7β-hydroxysitosterol with ChemAxon within MDL SD file.

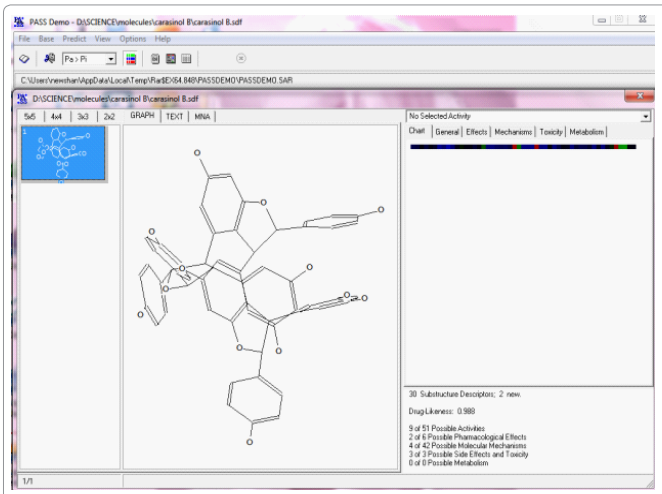

Figure 2: Platform and analysis of *Carasinol B* for it anticancer activity PASS software.

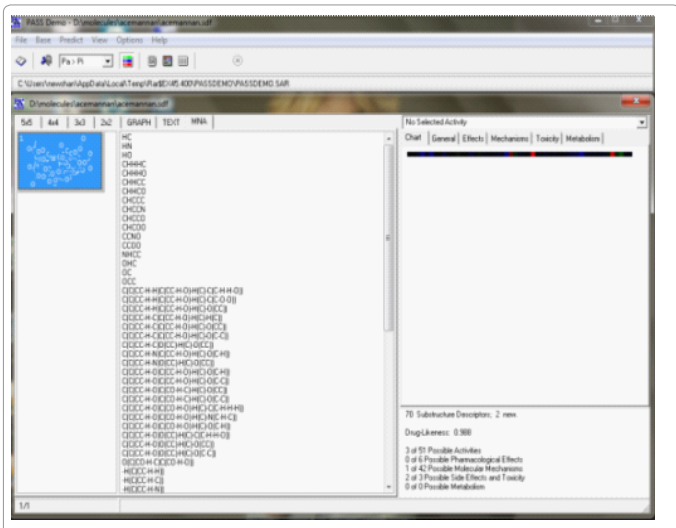

Figure 3: Platform and analysis of Acemannan by using PASS.

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, Topisomerase 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 antimitotic 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 isoflavone which can be isolated from *Trifolium pretense* [7] revealed that this agent has an antiproliferative effects, 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 super coiling during replication. Type I topoisomerases cut one strand of double-strand DNA, relax the strand and reanneal the strand [8]. *Kabophenol A* and *Carasinol B* are stilbene tetramers, which can be isolated from *Caragana chamague* 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.

	Molecules	Microtubule formation inhibitor	β-tubulin antagonists	Antimitotic activity	Drug likeness
1	Docetaxel	0.986	0.641	0.992	0.991
2	7-xylosyl-10-deacetyl paclitaxel	0.757	0.602	0.868	0.992

Table 1: PASS prediction of Docetaxel and 7-xylosyl-10-deacetyl paclitaxel.

	Molecules	Target	PASS activity	Drug likeness
1	Pseudobaptigenin	PTK Inhibitor	0.702	0.916
2	kobophenol A	Topisomerase I inhibitors	0.652	0.981
3	Carasinol B	Topisomerase I inhibitors	0.669	0.988
4	7β-hydroxysitosterol	Myc Inhibitor	0.657	0.986
5	Dehydrocostuslactone	Aromatase Inhibitor	0.656	0.995
6	Artemether	DNA synthesis inhibitor	0.801	0.996
7	Acemannan	Protein synthesis inhibitor	0.613	0.988

Table 2: PASS prediction of natural anticancer molecules.

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 *Sellaginella 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 *Artenisinin* 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 *Carasinol 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.

References

1. Strachan T, Read A (2011) Human Molecular Genetics. Fourth Edition.
2. Brunton L, Chabner B, Knollman B (2010) Goodman and Gilman's The pharmacological Basis of Therapeutics. 12th Edition.
3. Vaidya V, Dawkhar Sh (2010) A review of bioinformatics applications in breast cancer research. Journal of advanced bioinformatics application and research. 59-69.
4. Behrangi N, Hashemi N, Doustar Y, Borna H (2011) Camptothecins and their novel anticancer properties evaluated by using pass method. Advances in Environmental Biology 5: 2551-2556.
5. Lodish H, Berk A, Kaiser CA, Krieger M, Scott MP, et al. Molecular Cell Biology. 5th Edition.
6. Jiang S, Zu Y, Fu Y, Zhang Y, Efferth T (2008) Activation of the mitochondria-driven pathway of apoptosis in human PC-3 prostate cancer cells by a novel hydrophilic paclitaxel derivative, 7-xylosyl-10-deacetylpaclitaxel. Int J Oncol 33: 103-111.
7. Yanagihara K, Ito A, Toge T, Numoto M (1993) Antiproliferative effects of isoflavones on human cancer cell lines established from the gastrointestinal tract. Cancer Res 53: 5815-5821.
8. Hyde D (2009) Introduction to Genetics Principles.
9. Roh EM, Jin Q, Jin HG, Shin JE, Choi EJ, et al. (2010) Structural implication in cytotoxic effects of sterols from Sellaginella tamariscina. Arch Pharm Res 33: 1347-1353.
10. Walters WP, Stahl MT, Murcko MA (1998) Virtual screening: An overview. Drug Discovery Today 3: 160-178.
11. Jiao Y, Ge CM, Meng QH, Cao JP, Tong J, et al. (2007) Dihydroartemisinin is an inhibitor of ovarian cancer cell growth. Acta Pharmacol Sin 28: 1045-1056.
12. Ramamoorthy L, Tizard IR (1998) Induction of apoptosis in a macrophage cell line RAW 264.7 by acemannan, a beta-(1,4)-acetylated mannan. Mol Pharmacol 53: 415-421.
13. Tian CY, Hu CQ, Xu G, Song HY (2002) Assessment of estrogenic activity of natural compounds using improved E-screen assay. Acta Pharmacol Sin 23: 572-576.
14. Fedoreyev SA, Bulgakov VP, Grishchenko OV, Veselova MV, Krivoschekova OE, et al. (2008) Isoflavonoid composition of a callus culture of the relict tree Maackia amurensis Rupr. et Maxim. J Agric Food Chem 56: 7023-7031.
15. Miller JH, Singh AJ, Northcote PT (2010) Microtubule-stabilizing drugs from marine sponges: focus on peloruside A and zampanolide. Mar Drugs 8: 1059-1079.
16. Taraboletti G, Micheletti G, Dossi R, Borsotti P, Martinelli M, et al. (2005) Potential antagonism of tubulin-binding anticancer agents in combination therapies. Clin Cancer Res 11: 2720-2726.
17. Prochownik EV (2004) c-Myc as a therapeutic target in cancer. Expert Rev Anticancer Ther 4: 289-302.
18. Lee SR, Kwak JH, Park DS, Pyo S (2011) Protective effect of kobophenol A on nitric oxide-induced cell apoptosis in human osteoblast-like MG-63 cells: Involvement of JNK, NF-κB and AP-1 pathways. Int Immunopharmacol 11: 1251-1259.
19. Mishra RC (2011) Microtubule binding natural substances in cancer chemotherapy. Research Singpost 269-282.
20. Schmidt M, Bastians H (2007) Mitotic drug targets and the development of novel anti-mitotic anticancer drugs. Drug Resist Updat 10: 162-181.
21. Vita M, Henriksson M (2006) The Myc oncoprotein as a therapeutic target for human cancer. Semin Cancer Biol 16: 318-330.
22. Cheng K, Liang G, Hu C (2008) Acid-catalyzed epimerization of kobophenol A to carasinol B. Molecules 13: 938-942.
23. Jordan MA, Wilson L (2004) Microtubules as a target for anticancer drugs. Nat Rev Cancer 4: 253-265.
24. Ewesuedo RB, Ratain MJ (1997) Topoisomerase I Inhibitors. The oncologist 2: 359-364.
25. Cragg GM, Newman DJ (2005) Plants as a source of anti-cancer agents. J Ethnopharmacol 100: 72-79.
26. Kihara D, Yang YD, Hawkins T (2007) Bioinformatics resources for cancer research with an emphasis on gene function and structure prediction tools. Cancer Inform 2: 25-35.
27. Lankat-Buttgereit B, Göke R (2003) Programmed cell death protein 4 (pdcd4): a novel target for antineoplastic therapy? Biol Cell 95: 515-519.
28. Amin A, Gali-Muhtasib H, Ocker M, Schneider-Stock R (2009) Overview of Major Classes of Plant-Derived Anticancer Drugs. Int J Biomed Sci 5: 1-11.
29. Hermeking H (2003) The MYC oncogene as a cancer drug target. Curr Cancer Drug Targets 3: 163-175.
30. Chakraborti KA, Thilagavathi R (2003) Computer–Aided Design of Selective COX- 2 Inhibitors: Molecular Docking of Structurally Diverse Cyclooxygenase-2 Inhibitors using FlexX Method. J Mol Des 1: 000-000.
31. Passarge E (2007) Color of Atlas Genetics. 3rd Edition.
32. Alberts B, Johnson A, lewis J, et al. (2002) Biology of the cell. 4th Edition.