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Full Length Research Paper

Protein tyrosine kinase (PTK) as a novel target for some natural anti-cancer molecules extracted from plants

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For the fact that protein tyrosine kinases (PTKs) are important components of signal transduction pathway, they also are involved in regulating cell growth, differentiation and oncogenesis. Therefore, protein tyrosine kinases represent a potential target for cancer treatment. Drugs known as protein tyrosine kinase (PTK) inhibitors play a key role in developing therapeutic strategies for cancer therapy and plants are critical sources of natural PTK inhibitors. In the present study, we evaluated some natural anticancer molecules with PASS software in order to predict their possible targets involved in cancer. About 14 molecules (Afrormosin, Iriflogenin, Irigenin, Irisolidone, Irilone, biochanin A, Pseudobaptigenin, Pinosylvin, Galangin, Luteolin, Apigenin, Formononetin, Piceatannol and Daidzein) exhibited PTK inhibitor activity more than 0.6 theresholds. The results obtained reveal that Daidzein shows the highest PTK inhibitor activity with 0.780 score. However, Galangin has the lowest PTK inhibitory with 0.605 score. Furthermore, all of these compounds have CYP1A1 human substrate activity with score more than 0.6; therefore, Biochanin A and Daidzein with score 0.815 are the most potent CYP1A1 human substrate. In addition, all molecules had high druglikeness score and it means that they are been applied as drugs. Consequently, Biochanin A and Diadzein with 0.79 mean score are the most potent anticancer agents in our study.

Key words: Protein tyrosine kinase, plants, bioinformatics tools.

INTRODUCTION

In multicellular organisms, all aspects of cell behavior such as metabolism, movement, proliferation and differentiation are regulated by cell signaling. Signal transduction pathway transmits a signal into cell by a series of consecutive events that regulate the activity of a gene. Protein tyrosin kinases mediate the transduction and process of many extra-and intracellular signals. They are involved in regulating cell growth, differentiation as well as oncogenesis.

There are two general classes of protein tyrosin kinases: The receptor tyrosine kinase and receptor-associated tyrosine kinase. The receptor tyrosine kinase consists of an extracellular ligand binding domain and and intracellular catalytic domain which has tyrosine kinase activity. When a ligand is bound to the receptor, the various downstream effects including stimulation of other tyrosine kinases, elevation of intracellular calcium levels, activation of serine/threonine kinases, phospholipase C and phosphatidylinositol-3'-kinase, and ultimately changes in gene expression are going to occur. The receptor-associated tyrosine kinase interacts with the cytoplasmic domain of membrane protein in order to transmits signal from the membrane (Strachan and Read, 2011; Hyde et al., 2009).

Protein tyrosine kinases have enormous roles in cancer molecular pathogenesis, so currently they are as a potential target for anticancer drugs. There are two classes of protein tyrosine kinase inhibitors. One is bound to the ATPbinding site and the other is bound to the substrate binding site of the enzyme (Fabbro et al., 2002). Most of the anticancer drugs that target protein tyrosine kinase are extracted from plants, fruits or microorganisms (Brunton et al., 2011).

Bioinformatics is the mathematical, statistical and computing methods that aim to solve biological problems (Vaidya and Dawkha, 2010). Bioinformatics can be

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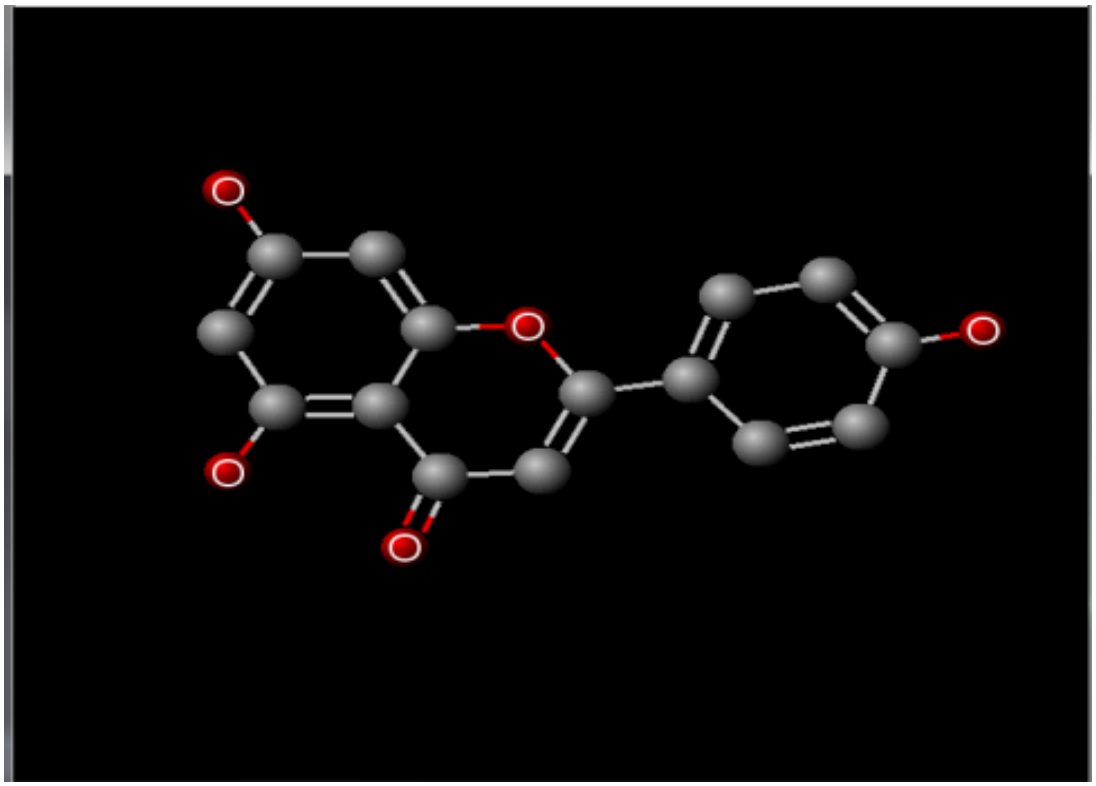

Figure 1. 3D structure of Apigenin with ChemAxon within MDL SD file.

applied in the field of medical sciences to know the molecular pathways of diseases. By developing sophisticated bioinformatics software such as prediction of activity spectra for substances (PASS), it is now possible to predict some targets of anticancer molecules on basis of the structure formula of a substance with high accuracy (Poroikov et al., 2003; Ali et al., 2011).

This study is focused on PASS score of some natural anticancer molecules and selected molecules based on specific target throughout cancer pathway. As a result, molecules which exhibited protein tyrosine kinase inhibitory with PASS score more than 0.6 were screened, and they are includes: Afrormosin, Iriflogenin, Irigenin, Irisolidone, Irilone, biochanin A, Pseudobaptigenin, Pinosylvin, Galangin, Luteolin, Apigenin, Formononetin, Piceatannol and Daidzein. Although Iriflogenin, Irigenin, Irisolidone, Irilone are isoflavones isolated from rhizome of *Iris germanica*, other compounds are extracted from different plants around the world (Ludwiczuk et al., 2011; Entezari et al., 2009).

MATERIALS AND METHODS

Data

A paractical database is the main step in bioinformatics projects. Collections of data from Pubmed database were accomplished with general keyword “anticancer”. Most data were gathered from 2010 papers; therefore, anticancer molecules were extracted from these papers, and their targets in apoptotic pathway defined. 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, semi-synthetic agents, synthetic agents and finally ungrouped anticancer agents which their origins were unknown (Behrangi et al., 2011).

Structure

Structural formula of these molecules were investigated from Chemspider, Pubcheme 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 as well (Figure 1).

Software

Predicition of activity spectra for substance (PASS) 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 with over 80% accuracy and has capability to predict many types of activity

Table 1. Pa and Pi of PTK inhibitory, CYP1A1 human substrate and drug likeness of molecules.

Label	Molecule	PASS activity (PTK Inhibitory)	PASS inactivity (PTK inhibitory)	PASS activity (CYP1A1 human substrate)	PASS inactivity (CYP1A1 human substrate)	Drug likeness
A	Afrormosin	0.699	0.004	0.738	0.005	0.865
B	Apigenin	0.638	0.005	0.716	0.005	0.940
C	Biochanin A	0.758	0.003	0.815	0.004	0.887
D	Daidzein	0.780	0.002	0.814	0.004	0.857
E	Formononetin	0.724	0.003	0.759	0.005	0.817
F	Galangin	0.605	0.006	0.678	0.006	0.957
G	Iriflogenin	0.654	0.005	0.641	0.007	0.968
H	Irigenin	0.706	0.004	0.710	0.005	0.928
I	Irilone	0.701	0.004	0.683	0.006	0.978
J	Irisolidone	0.657	0.005	0.696	0.006	0.983
K	Luteolin	0.635	0.005	0.707	0.006	0.959
L	Piceatannol	0.657	0.005	0.679	0.006	0.795
M	Pinosylvin	0.638	0.005	0.686	0.006	0.683
N	Pseudobaptigenin	0.702	0.004	0.689	0.006	0.916

for a new substance.

PASS utilizes input data with molecular structure *Protein Data Bank (PDB), Tripos MOL2*, *MDL MOL* and *SD file* formats for representing 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 is the probabilities of being active and close to 1.000, and Pi is 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, and molecules with Pa more than 0.6 have been selected on basis of protein tyrosine kinase inhibitory in cancer pathway.

RESULTS

Almost 242 molecular structures were collected from PubChem, Chemspider database and Google search. In addition, these compounds were evaluated with PASS in order to screen compounds with high anticancer activity PASS software also has capability to express the drug-likeness of molecules .

Drug-likeness referred to specific score estimated from the molecular structure and indicate that specific molecule have some proportional properties which can be active biologically or might show therapeutic potential and cytotoxicity (Walters et al., 1998).

In this study, about 14 molecules revealed high PTK inhibitor bioactivity (Pa>0.6); therefore, it is predicted that indicated agents can inhibit protein tyrosine kinase with high strength and by increasing the Pa score of them ,their strength will be improved simultaneously. Thus, according to Table 1, Daidzein with Pa 0.780 is the most potent PTK inhibitor in our research. In our research, we have confronted interesting issue that all of our PTK inhibitor agents are as CYP1A1 human substrate and they exhibit these properties with Pa score more than 0.6. Consequently, Daidzein exhibited the highest P activity (0.814) compare to other molecules. As can be seen from Table 1, Irisolidone with score 0.983 have the highest drug-likeness score and it means that this agent might posses functional groups or have physical properties which is consistent with most of known drugs (Walters et al., 1998).

DISCUSSION

Predication of activity spectra for substances (PASS) software capable to anticipate more than 1500 pharmacological effect can be efficiently applied to find new targets for some ligands to reveal new biological activity of various substances (Lagunin et al., 2000; Jin et al., 2010). As this study has focused on anticancer molecules, we tried to find out efficient target in cancer pathway and screen molecules on basis of their strength in specified activity.

Tyrosine Kinase is an enzyme which transports phosphates from ATP to a proteins tyrosine residue. Therefore, a tyrosene kinase inhibitor prevents the phosphate groups from being transferred. In many cases of human malignancies, some mutations activate proten tyrosine kinase constitutively in order to implicate malignant transformation. Thus, protein tyrosine kinase is an appropriate target for cancer treatment. In this study, we screened molecules which have Pa>0.6 and Pi<0.006; consequently, about 14 natural substances have been selected according to this spectrum. It is notice worthy that PTK inhibitory of some of selected substances have been exhibited by previous research. For example, Byun et al. (2010) revealed that *Luteolin* is a flavonoid which binds directly to PKC (epsilon) and Src

in ATP-competitive manner, in order to inhibits PKC(epsilon) and Src kinase activity (Gyémánt et al., 2005). In addition, as Yin et al. (2001) demonstrated, Apigenin decreases growth factor receptor (EGF-R) tyrosine phosphorylation and phosphorylation of ERK mitogen-activated protein (MAP) kinase. Likewise, PASS results (Table 1) were so consistent with previous research and demonstrated molecules showed high Pa too. For instance, Luteolin and Apigenin with Pa 0.635 and 0.638 respectively are as promising PTK inhibitor agents. Moreover, Daidzein has the most potent PTK inhibitor activity with 0.780 score, in contrast Galangin exhibits the lowest PTK inhibitory with score 0.605 (Heo et al., 2001). Biochanin A with 0.758 score is the second strong protein tyrosine kinase inhibitor agent.

Interestingly, all of the 14 molecules with PTK inhibitor activity show CYP1A1 human substrate activity too. As Cytochrome P450 1A1 isoenzyme involving in metabolic conversion of paracarcinogens into carcinogens, thus Cyp1A1 is as a target for cancer chemoprevention. Previous research also shows that some of indicated molecules are CYP1A1 Human substaret. For example, Wollenweber et al. (2003) exhibited Iriflogenin, Irigenin, Irisolidone and Irilone are as potent inhibitors of cytochrome P450 1A enzyme. Our study demonstrated that Biochanin A and Daidzein with score 0.815 are the most potent CYP1A1 human substrate and they show this property with high strength (Moon et al., 2008; Sehdev et al., 2009; Peterson and Barnes, 1993).

In conclusion, the Table 1 clearly shows that all of the 14 natural anticancer molecules are as a potent protein tyrosine kinase inhibitor and CYP1A1 human substrate. In addition, their high drug likeness candidate them as functional anticancer drugs which can have therapeutic effects. Because these molecules are extracted from nature, we can reduce side effect of chemotherapeutic drugs efficiently, but application of these drugs in clinic demands *in vitro* and *in vivo* experiments and we hope that future experimental research can candidate them as known anticancer drugs.

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