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PREDICTION OF ANTICANCER ACTIVITY OF POTENTIAL ANTICANCER COMPOUNDS USING PASS ONLINE SOFTWARE

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Abstract

Background: Cancer is defined as abnormal and uncontrolled division of body's own cell. The Anticancer drug will either kill the cancerous cell or modify their growth. In the present scenario, It is the second most killer of people in country where one in three people are diagnosed with cancer. Due to advancement in research field, use of animal was also increased for evaluation of new drug. Objective: Keeping this in mind, PASS (Prediction of activity spectra of substances), a software which provide an informative predictive data for different pharmacological activity of compounds without the use of animals. It justifies the 5R'S ethics (Replacement, Reduction, Refinement, Rehabilitation and reuse) for *in vivo* evaluation. The core purpose of the study was to predict the anticancer activity of potential compound of DPP-4 inhibitor using PASS software. Methods: To predict the pharmacological activity of anticancer compound, canonical smiles of compound were obtained from pubchem web page. The canonical smiles of each compound were used in PASS software for prediction of pharmacological activity, so that the compound which show the best result can further be used as a in vivo study against anti-cancer drug. Result: From the screened compounds, it was found that anagliptin and quinovic acid, which is a DPP-4 inhibitor used for type 2 diabetics can also be used for anticancer activity. Conclusion: Lupeol and Quinovic acid show good Pa value and it can be further evaluated as *in vivo* anticancer drug evaluation.

Keywords: Anticancer activity, PASS software, 5R'S ethics, DPP-4 inhibitors

Introduction

Cancer is a broad term consist of a group of disease with irregular cell growth having the potential to migrate in other part of body (Sharma *et al*., 2011). Cancer cell invade healthy cell in body. They form tumor. A tumor is a group of cells that have undergone uncontrolled growth and form a lump (Adami *et al*., 2008; Connolly *et al*., 2000; Cullen *et al*., 2002). In today's scenario it is the second largest killer disease. In normal cell gene function by growth regulation, its maturity and death of the cell. Genetic change can occur by insertion or deletion of entire chromosome or gene sequence varies in one base pair i.e. transition (Purine is replaced by purine and vice versa) or transversion (Purine is replaced by pyrimidine and vice versa). Oncogene and Tumor suppressor gene are the two different type of gene which are affected by genetic change. Oncogene are the cancer-causing gene. The proto oncogene is the normal gene that convert into oncogene due to mutation. They also alter the normal gene through mutation (Sarkar *et al*., 2018). Tumor suppressor gene are also known as anti-oncogene which regulate a cell during cell division and replication. When this gene gets mutated, it results in loss of its function. In cancer patient the oncogene level is high and tumor suppressor gene is retarded (Cullen *et al*., 2002).

Diabetics has concurred our society and made an impact to every part of our country (Bhatia *et al*., 2014). Many herbal plant posses the potential to treat diabetics (Singh *et al*., 2019) But human esterase some time interect with the phytochemical of anticancer compound (Grewal *et al*., 2014). Musroom possese anticancer properties (Patel *et al*., 2012). Cereal bean along with antioxidant possess anticancer properties (Patel *et al*., 2012). Anticancer drugs are also known as antineoplastic drug. Tremendous research is carried out in anticancer therapy (Saluja *et al*., 2019). There are various interactions of anticancer drug like p53-Mdm2 (Nayak *et al*., 2018). It is effective in treatment of malignant or cancerous disease (Nanda *et al*., 2018). There are several classes of anticancer drug, alkylating agent, anti-metabolites, natural product and hormone (Fig. 1). Apart from these class there are some other drug which does not fall in this category of class of have anticancer properties. The type and location of cancer, severity of cancer, side effect associated with the drug are factor to be consider before a drug was given (Bhatia *et al*., 2012). Anticancer drugs are given mostly given in intramuscular route, some drugs are also given in oral route and intravenous route.

Anticancer drugs are generally toxic to normal cell and cause numerous side effect. Some of these are hair loss, sores in mouth and other mucous membrane, nausea, vomiting. Bone marrow toxicity is one of the major side effects which cause anemia and decreases resistance to infectious agent. These side effect can be minimized by either reducing the doses of drug or changing the regimen of drugs (Thiengsusuk *et al*., 2019).

Some antidiabetic drug of class DPP-4 inhibitor, type 2 also possess anticancer poroperties.Antidiabetic drug act by reducing the blood glucose level in blood (Singh *et al*., 2010). Like in type 2 diabetic alpha amylase inhibitor was given (Bashary *et al*., 2020). Some dendrimer also possess antidibetic properties (Mishra *et al*., 2019) But still the research are also going for the treatment of diabetic (Khursheed *et al*., 2019). There is prediction of readmission rate of diabetic patient (Sharma *et al*., 2019). Curcumin also possess diabetic properties (Garg *et al*., 2019). PPARγ found to be natural agnosit (Shafi *et al*., 2019). Some pharmaceutical intervention was found for management of diabetic mellitus (Khatik *et al*., 2019). The development of screening model for cancer treatment is indispensable for the improvement of cancer treatment, to know the potential of anticancer drug (Kumar *et al*., 2019). Anticancer drugs are

tested in both *in vivo* and *in vitro* method to know the potential of drug (Alsamman and El-masry, 2017). We can design anticancer drug by computer (Kumari *et al*., 2011).

Many drugs have been reported in the literature to have strong anti-cancer potential (Anand *et al*., 2019). Lupeol is a triterpinod which is present in remedial plants which has biological activity for cure of human disease (Pathania *et al*., 2014). Nux-vominca was also reported to show anticancer activity (Sah *et al*., 2016). Lupeol was studied *in vitro* and reported that it has cytotoxic proterties against various cancer cell line. Lupeol found to be effective against MCF-7 Cell (Human breast cancer cell line) by the process of staining with Ethidium Bromide. *In vivo* study wass also done in which lupeol was used as antiinflammatory agent in mouse model of arthritis. It was found that lupeol suppress the CD4 T cell and modulate the phagocytic activity of T lymphocyte in the mouse model (Bani *et al*., 2006; Pitchai *et al*., 2014).

Another potential compound, quinovic acid, is a glycoside which is was a purified fraction from U tomentosa . Various study was done for therapeutic activity of quinovic acid. A *in vivo* study was conducted in which the potential anticancer effect was seen by the use of mouse model. The result was found that there was decrease in IL-1 alpha and it also downregulate P2X7 receptor (Dietrich *et al*., 2015)

Cirsimaritin is an flavone derived from *Lithocarpus dealbatus*. *In vitro* study was done on cirsimaritin which says that there was increase in melanin and tyrosine activity. It was also found that it also have ultraviolet photoprotective activity. It upregulate the expresstion of MITF (Microphthalmia – associated trancription factor). These activity was observed in murine B16F10 melonoma cell (Kim *et al*., 2015)

Pyrrolopyrimidine have potent anticancer properties by the name of molecule PP-13. Various in vivo and in vitro studies were conducted. In an in vitro study, it was found that PP-13 have cytotoxic effect on various cancer cell line. It also cause direct death of cell, aneuploidy by mitotic blockade. *In vivo* study PP-13 molecule helps in reducing the tumour growth without any side effect in chicken embroyo (Gilson *et al*., 2017). There are many other compound having anticancer properties (Kaur *et al*., 2019). Many plant in our surrounding possess anticancer proterties like guggle (Singh *et al*., 2019), Sinomenium acutum (Gupta *et al*., 2019), Fisetin (Kumar *et al*., 2019), Ocimum tenuiflorum (Sharma *et al*., 2017), epigallocatechin gallate (Anand *et al*., 2017), Crataeva Nurvala Bark (Kaur *et al*., 2017).

PASS is a computer-based software provide different information about biological activity of chemical compound based on their chemical structure (Sharma *et al*., 2018). The current version of PASS can predict more than 3750 biological activity, biochemical mode of action by the help of canonical SMILE (Simplified molecular input line entry system (Habibyar *et al*., 2016). It gives accuracy of 95%. It predicts the activity in term of probability; probable activity (pa) and probable inactivity(pi). The values are in the range of 0.000 – 1.000 (Kumar *et al*., 2018). The activity of chemical compound is considered only if pa>pi. The compound having pa value greater than 0.7 are consider to have better pharmacological action. Similarly, compound having less than 0.7 have less probability of observing the activity (Habibyar *et al*., 2016).

The present study incorporated the use of PASS software for exploration of pharmacological potential of selected phytochemical compounds in the treatment of cancer, with respect to various target (Prashar *et al*., 2019; Usman *et al*., 2019).Various engineering work was also done in computer for site specific delivery of anticancer drug was designed (Nayak *et al*., 2017).

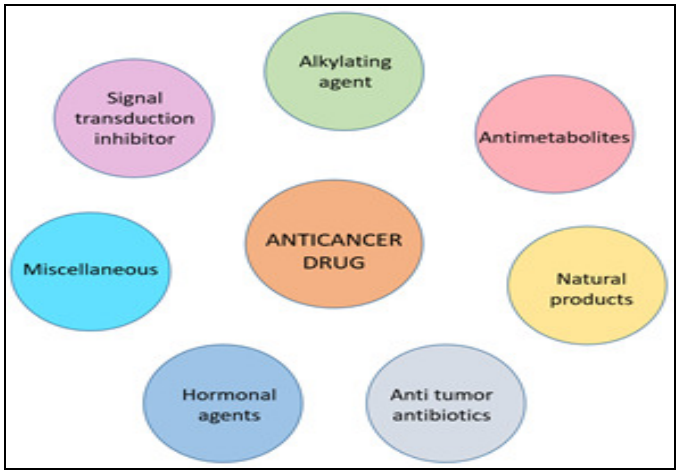

Fig. 1: Different categories of anti-cancer drugs

Materials and Methods

Several compounds were selected on the basis of existing literature, suggesting their applicability in the treatment of anticancer drug. One marketed drug was selected to predict the biological activity spectra. The canonical SMILE which works as a formula of these phytochemical and marked drug were obtained from PubMed (www.pubchem.ncbi. nlm.nih.gov) (table 1). The canonical SMILES of individual compound were pasted into the PASS software for the prediction of DPP-4 inhibition, type 2 diabetic inhibitor and anticancer activity. The probable activity (Pa) and probable inactivity (Pi) values of each compound were recorded and compared with the standard drug (Sitagliptin).

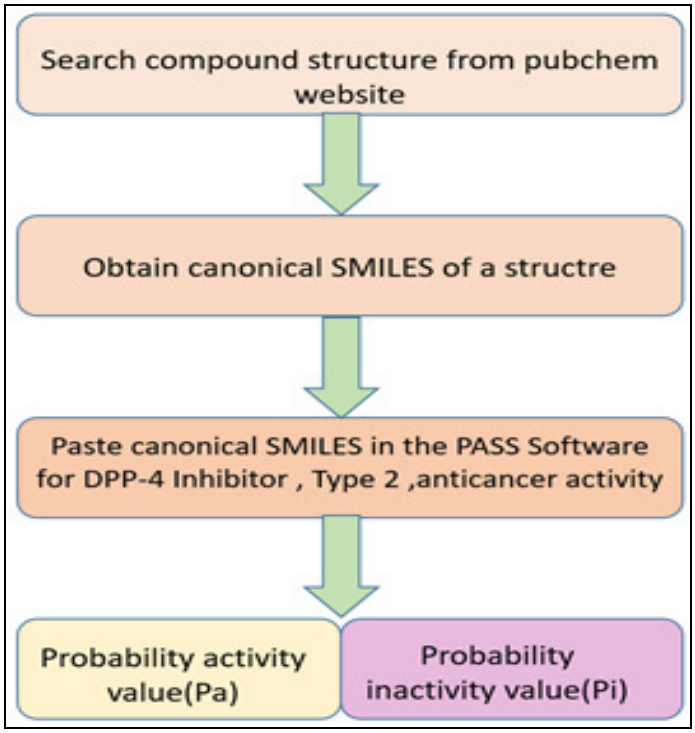

Fig. 2: Flow diagram of *in silico* evaluation of selected compounds

Result and Discussion

Cancer is a serious disorder now a day. In India nearly 4 lakhs of people are being affected by cancer every year(Sharma.et.all,2010). PASS is an online program that can be used for predicting the biological activity of a chemical compounds on the basis of chemical composition and interaction with different targets.One marketed drug, sitagliptan, which is used in case of diabetics has the anticancer properties. It is a DPP-4 inhibitor enzyme have both in vivo and in vitro activities and also having antioxidant properties. (Usman *et al*.,2019). It has been characterized as an apoptotic agent on pancreatic cancer cell (Amritha *et al*., 2015).

Using PASS online software, DPP-4 inhibition, type-2 anti-diabetic and anticancer activities of selected chemical compounds along with marketed compound were predicted (Anand *et al*., 2017). The biological activities of the chemical compound and marketed drug i.e. Sitagliptan are represented in table 2 and fig. 3. From the above chemical compounds, the compound having high DPP-4 inhibitor activity next to sitagliptan is quinovic acid and the least activity of

DPP-4 inhibitory value was shown by compound cyclohexylamine. The pattern of DPP-4 inhibitor is quinovic acid > anagliptin > DA-1229 > BI 1356 > Diprotin A > Diprotin B. Other compounds which are also used to treat type 2 diabetic also show anticancer activities. The castanospernum possess high activity of type 2, next to sitagliptan. The least activity of type 2 was show by chalconaringenin. The pattern of type 2 is castanospernum > DA-1229 > quinovic acid > anagliptin > BI 1356 > diprotin A > cirsimaritin > diprotin B > pyrrolopyrimidine > aureusidin > chalconaringenin.

The comparison is done with anticancer activity and it was found that quinovic acid and lupeol, which has high DPP-4 inhibitor activity and type 2 activity, possess anticancer activity more than sitagliptan. The pattern of anticancer activity of compound is lupeol > quinovic acid > cirsimaritin > chalconaringenin > diprotin A > pyrrolopyrimidine > aureusidin > anagliptin > DA-1229 > sitagliptan.

It was found that among the screened compounds, quinovic acid, stigmasterol, lupeol, diprotin A, carnosol, cirsimaritin, chalconaringenin, anagliptin and aureuside were found to have anticancer activity more than the standard drug, i.e. sitagliptan.

Conclusion

It was concluded that the drug which possess anti-diabetic properties also have anticancer properties. Lupeol and quinovic acid possess good anticancer properties of Pa value 0.954 and 0.891 respectively.

Hence by the use of PASS software, we can find the pharmacological action of compound. These compounds can be further investigated for the anticancer activity application of in vivo and in vitro study. Hence from the above study, PASS, an online software help in prediction of pharmacological action of compounds. This software also aid's 5R ethics for animal usage before in vivo study which not only save money and time, but also it save number of animals (Khurana.et.al,2018)

Table 1: Canonical SMILES of selected compounds

Name of compound	Conical smiles
BI 1356	CC#CCN1C2=C(N=C1N3CCCC(C3)N)N(C(=O)N(C2=O)CC4=NC5=CC=CC=C5C(=N4)C)C
Cyclohexylamine	C1CCC(CC1)N
DA-1229	CC(C)(C)OCC1C(=O)NCCN1C(=O)CC(CC2=CC(=C(C=C2F)F)F)N
Quinovic acid	CC1CCC2(CCC3(C(=CCC4C3(CCC5C4(CCC(C5(C)C)O)C)C)C2C1C)C(=O)O)C(=O)O
Stigmasterol	CCC(C=CC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C
Lupeol	CC(=C)C1CCC2(C1C3CCC4C5(CCC(C(C5CCC4(C3(CC2)C)C)(C)C)O)C)C
Pyrrolopyrimidine	C1=CNC2=CN=CN=C21
Berberine	COC1=C(C2=C[N+]3=C(C=C2C=C1)C4=CC5=C(C=C4CC3)OCO5)OC
Diprotin A	CCC(C)C(C(=O)N1CCCC1C(=O)NC(C(C)CC)C(=O)O)N
Diprotin B	CC(C)CC(C(=O)O)NC(=O)C1CCCN1C(=O)C(C(C)C)N
Castanospermine	C1CN2CC(C(C(C2C1O)O)O)O
Carnosol	CC(C)C1=C(C(=C2C(=C1)C3CC4C2(CCCC4(C)C)C(=O)O3)O)O
Cirsimaritin	COC1=C(C(=C2C(=C1)OC(=CC2=O)C3=CC=C(C=C3)O)O)OC
Chalconaringenin	C1=CC(=CC=C1C=CC(=O)C2=C(C=C(C=C2O)O)O)O
Aureusidin	C1=CC(=C(C=C1C=C2C(=O)C3=C(C=C(C=C3O2)O)O)O)O
Anagliptin	CC1=NN2C=C(C=NC2=C1)C(=O)NCC(C)(C)NCC(=O)N3CCCC3C#N
Sitagliptan	C1CN2C(=NN=C2C(F)(F)F)CN1C(=O)CC(CC3=CC(=C(C=C3F)F)F)N

Table 2: Pa and Pi values of different compounds predicted using PASS online software (continued)

S. No.	Name of compound	DPP-4 Inhibitor Pa	DPP-4 Inhibitor Pi	Type II Pa	Type II Pi	Anticancer Pa	Anticancer Pi
1	BI 1356	0.204	0.002	0.382	0.048	0	0
2	Cyclohexylamine DPP-4	0.01	0.004	0.206	0.056	0.218	0.066
3	DA-1229	0.293	0.002	0.557	0.008	0.315	0.007
4	Quinovic acid	0.535	0.009	0.535	0.009	0.891	0.005
5	Stigmasterol	0	0	0	0	0.405	0.015
6	Lupeol	0	0	0	0	0.954	0.004

7	Pyrrolopyrimidine	0	0	0.228	0.095	0.497	0.072
8	Berberine	0	0	0	0	0.203	0.003
9	Diprotin A	0.514	0.003	0.314	0.029	0.598	0.110
10	Diprotin B	0.127	0.004	0.246	0.043	0.228	0.136
11	Castanospernum	0	0	0.649	0.009	0.236	0.197
12	Carnosol	0	0	0	0	0.793	0.013
13	Cirsimaritin	0	0	0.295	0.042	0.815	0.01
14	Chalconaringenin	0	0	0.155	0.023	0.773	0.015
15	Aureusidin	0	0	0.184	0.153	0.382	0.034
16	Anagliptin	0.353	0.002	0.502	0.010	0.363	0.037
17	Sitagliptan	0.675	0.001	0.829	0.004	0.283	0.122

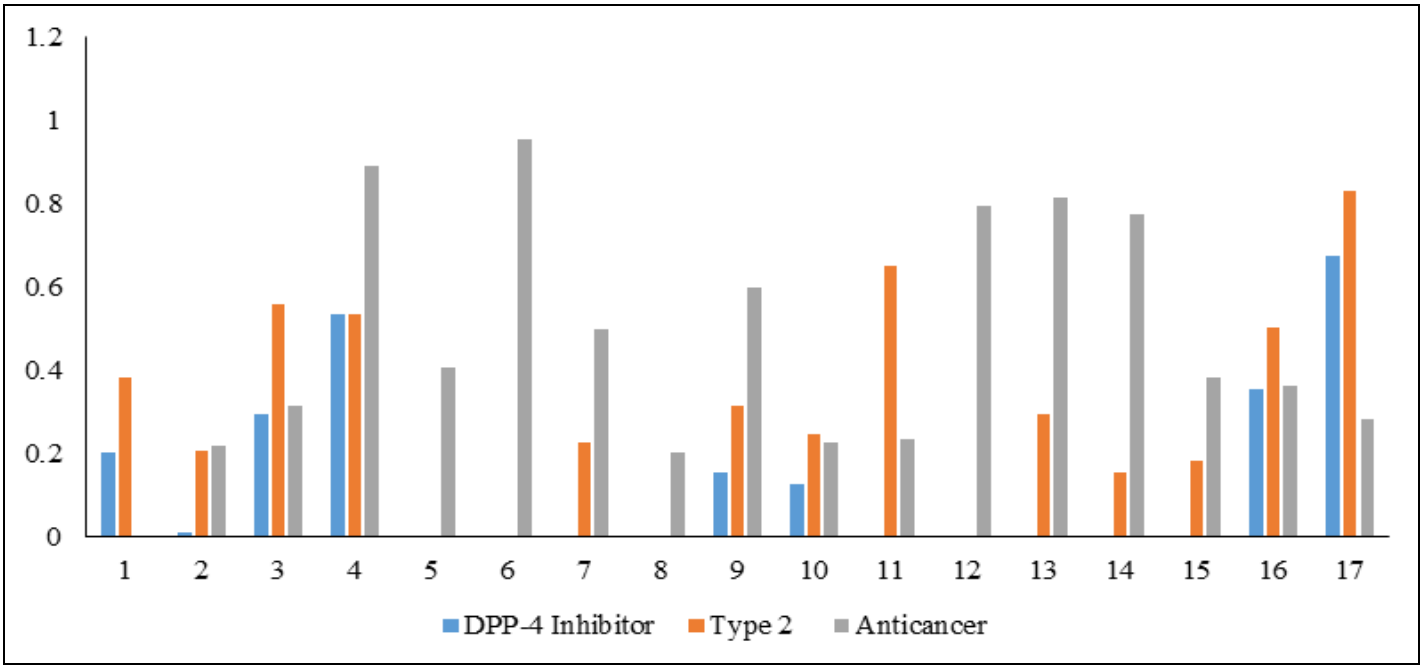

Fig. 3: Pa values for DPP-4 inhibitory, type 2 anti-diabetic and anti-cancer activities of different compounds using PASS

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