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Novel anticancer compounds from plant sources

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ABSTRACT

Plants remain a significant basis of new drugs and new drug leads to the new chemical entities. Plant based drug discovery give rise to the development of anti-cancer and anti-proliferative agents, and continues to add to the new leads in clinical trials. Products of plant drugs play a dominant role in pharmaceutical care and in treatment of various diseases. Several plant-derived compounds are positive results in cancer treatment. There are several classes of plant-derived cytotoxic natural products studied for further improvement and development of drugs. New anticancer drugs derived from research on plant antitumor agents will be continuously discovered. The basic aim of this research article is to explore the potential of newly discovered anticancer compounds from medicinal plants, as a lead for anticancer drug development. It will be helpful to explore the medicinal value of plants and for new drug discovery from them for the researchers and scientists around the globe. In search of novel anti-cancer compounds I have selected two different medicinal plants *Elettaria cardamomum and Ferula assa-foetida.*

Keywords: Cancer, Anti-cancer agents, Medicinal plants, *Elettaria cardamomum* and *Ferula assa-foetida* leaves.

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INTRODUCTION

Cancer is the abnormal growth of cells in our bodies that can lead to death. Cancer cells usually invade and destroy normal cells [1]. Every year, millions of people are diagnosed with cancer, leading to death. According to the American Cancer Society, deaths arising from cancer constitute 2%–3% of the annual deaths recorded worldwide. Thus cancer kills about 3.5 million people annually all over the world. Several antitumor agents are used to treat cancer, but they cause toxicity that limits their usage [2,3].

Because of the high mortality rate associated with cancer, and because of the serious side effects of chemotherapy and radiation therapy, many cancer patients seek alternative and/or complementary methods of treatment. Recent research revolves around the urgency to develop suitable chemotherapy for the treatment of cancer with no toxic effects [4]. Plants have been used for treating various diseases of human beings and animals since time immemorial.

Natural sources of antioxidants

The opposing effects of oxidative stress on human health have become a serious issue. Medicinal plants have great antioxidant potential which is because of their contents of variable phyto constituents. A large number of experiments have been performed concerning the antioxidant activity of several plant extracts. The results of these experiments reveal that, the activity is due to several secondary metabolites especially, e.g., phenolic compounds (tannins, flavonoids, anthrocyanins, chalcones, xanthones, liganans, depsides, and depsidones), terpenes (sesquterpens and diterpines), alkaloids, and organic sulfur compounds [5,6]

Cancer Study

Cancer is a complex disease that is normally associated with a wide range of escalating effects both at the molecular and cellular levels. It therefore seems unlikely that chemoprevention follows simplistic rules and formulations. The old saying **"Prevention is always better than cure"** is particularly true in the case of cancer where a cure, if at all possible, is associated with high cytotoxic loads and/or invasive procedures [7,8]

Cancer is a major public health problem worldwide with millions of new cancer patients diagnosed each year and many deaths resulting from this disease [9] Cancer is fundamentally a disease of regulation of tissue growth. In order for a normal cell to transform into a cancer cell, genes which regulate cell growth and differentiation must be altered [10] Tumor suppressor genes are often disabled by cancer-promoting genetic changes. Typically, changes in many genes are required to transform a normal cell into a cancer cell [11.]

What causes cancer?

Cancer is caused by both external factors (tobacco, chemicals, radiation and infectious organisms) and internal factors (inherited mutations, hormones, immune conditions and mutations that occur from metabolism). Diet derived natural products will be potential candidates for this purpose [12]

Several classes of anticancer drugs have been developed and many of them are of natural origin. However, most of the currently used anticancer drugs cause undesirable side effects due to lack of tumor specificity and multidrug resistance. Therefore the search for potent, safe and selective anticancer compounds is crucial for new drug development in cancer research. Natural products, due to their structural diversity, provide excellent templates for the construction of novel compounds [13,14]. It is well established that plants have been a useful source of clinically relevant antitumor compounds [15]. For example, Hartwell has collected data on about 3000 plants, those of which possess anticancer properties are subsequently used as potent anticancer drugs [16-18].

The use of plant extracts and derived products in the treatment of cancers is of exceptional value in the control of malignancies, due to the fact that most of the anticancer drugs severely affect the normal cells. It has been recommended that ethnopharmacological usages, such as immune and skin disorders, inflammatory, infectious, parasitic and viral diseases be taken into account when selecting plants used to treat cancer, since these reflect disease states bearing relevance to cancer or cancer symptoms[19-21]

Plant secondary metabolites and their semi-synthetic derivatives continue to play an important role in anticancer drug therapy [22]. These include vinblastine, vincristine, the camptothecin derivatives, topotecan and irinotecan, etoposide, derived from epipodophyllotoxin and paclitaxel (taxol). Sixty percent of currently used anticancer agents are derived in one way or another from natural sources [23]. In light of the continuing need for effective anticancer agents, and the association of fruit and vegetable consumption with reduced cancer risk, edible plants are increasingly considered as sources of anticancer drugs [24-25]

Plant derived anticancer agents in clinical use

The isolation of the vinca alkaloids, vinblastine and vincristine from the Madagascar periwinkle, *Catharanthus roseus* G. Don. introduced a new era of the use of plant material as anticancer agents. They were the first agents to advance into clinical use for the treatment of cancer [26] **.** Vinblastine and vincristine are primarily used in combination with other cancer chemotherapeutic drugs for the treatment of a variety of cancers, including leukemia, lymphomas, advanced testicular cancer, breast and lung cancers and Kaposi‟s sarcoma.

The discovery of paclitaxel (Taxol) from the bark of the Pacific Yew, *Taxus brevifolia* Nutt. is another evidence of the success in natural product drug discovery. *Taxus baccata* was reported to be used in the Indian Ayurvedic medicine for the treatment of cancer.

Epipodophyllotoxin is an isomer of podophyllotoxin, which was isolated as the active anti-tumor agent from the roots of *Podophyllum* species, *Podophyllum peltatum* Linnaeus and *Podophyllum emodi* Wallich [27]. Etoposide and teniposide are two semi-synthetic derivatives of epipodophyllotoxin and are used in the treatment of lymphomas and bronchial and testicular cancers [28]. Homoharringtonine, isolated from the Chinese tree *Cephalotaxus harringtonia* var. *drupacea* (Sieb and Zucc.), is another plant-derived agent in clinical use [29]. A racemic mixture of harringtonine and homoharringtonine has been used successfully in China for the treatment of acute myelogenous leukemia and chronic myelogenous leukemia [30-31]. Interesting patterns of differential cytotoxicity have been associated with known classes of compounds, such as cardenolides, lignans or quassinoids [32] In any cancer drug discovery program, a paradigm based on ethnobotanical and ethnopharmacological data would be more economical and beneficial in identifying potential anticancer molecules than mass screening of plant species [33] Natural products have been regarded as important sources of potential chemotherapeutic agents and many anticancer drugs have originated from natural sources [34]

Anticancer medicinal plants from India

Anticancer properties of many natural compounds isolated from different Indian plant extracts have been reported. Research is being carried out throughout the world to find a lead compound which can block the development of cancer in humans. Nature has always been a great contributor towards this goal. Plant-derived natural products such as flavonoids, terpenoids and steroids have received considerable attention due to their diverse pharmacological properties, which include cytotoxic and chemopreventive effects [40]

The isolation of the vinca alkaloids, vinblastine and vincristine from the Madagascar periwinkle, *Catharanthus roseus* introduced a new era in the use of plant material as anticancer agents. They were the first agents to advance into clinical use for the treatment of cancer [26] The medicinal plants contain many antioxidants such as vitamins (A, C, E, K), carotenoids, flavonoids (flavones, isoflavones, flavonones, anthocyanins, catenchins, isocatechins), polyphenols (ellagic acid, gallic acid, tannins), saponins, enzymes and minerals (selenium, copper, manganese, zinc, chromium, iodine, etc) [39] These plants continue to be used against various types of tumours such as sarcoma, lymphoma, carcinoma and leukemia. Many of these medicinal plants have been found to be very effective in experimental as well as clinical cases of tumours/cancers.

Flavonoids are a group of more than 4000 polyphenolic compounds that occur naturally in foods of plant origin. These polyphenolic compounds display a remarkable spectrumof biological activities including those that might be able to influence processes that are dysregulated during cancer development. These include, for example, antiallergic, anti-inflammatory, antioxidant, antimutagenic, anticarcinogenic, and modulation of enzymatic activities.[34-37] as given in table 1.

Molecular Docking:

There are many databases available for information regarding chemical compounds and their various features. **Pubchem** (http://pubchem.ncbi.nlm.nih.gov/): It is a repository of small molecules detailing their structure and activities. The Pubchem project is created and maintained by National center of biotechnological information which is a part of National institute of health. Pubchem contains three main databases. Substance database (primary accession-SID) contains contributed sample descriptions provided by depositors, whereas the Compound database (primary accession-CID) contains unique chemical structures derived from the substance depositions.

Drug bank:

Drug Bank is a diverse bio and cheminformatics database quantitative, molecular-information about drugs and drug targets molecules. Drug bank database contains the information which is designed by mixing the information about molecular biology information from Swiss-prot, NCBI, from different chemistry text books. It has around more than 4100 drug molecules matching to more than 12,000 different brand name and synonym.

Ligand:

It is a database and chemical compounds and pathways that occur in biological reactions. This database is mainly composed of three main database or sections namely “compound” section for information about metabolites and small molecule chemical compounds.”Reaction” section for collection of substrate and product reactions representing metabolic and other reactions. There is another section “Enzyme” which contains information about many different enzyme molecules.[50] In this database the COMPOUND and ENZYME sections are based on flat-files for information storing and the data format of each section is equivalent to that of GenBank. Compound and reaction sections are managed as MDB and RXN formats. The COMPOUND section of this LIGAND database was originally made by extracting different chemical compounds from the metabolic pathways of the KEGG, PATHWAY database. They are also trying to add many drug related information to the chemicals. This database can be accessed at http://www.genome.ad.jp/ligand/. In our study

we have selected Luteolin, (±)-α-Pinene (Alpha pinene), FERULIC ACID, QUERCITINE, INDOLE 3 CARBAZOL as Ligands and TTR (biomarker), Tankyrase, PPAR gamma ligand, Human Cytochrome P450, Enzymes S-ADENOSYL-L-HOMOCYSTEINE (DNA METHYLATION), BETA-D-MANNOSE, Protein kinase (PK) SELENOMETHIONINE, (all associated with Cancer) as Receptors.

MATERIALS AND METHOD

Molecular docking and Docking Tools.

DOCK BLASTER

DOCK Blaster is a free service for running docking screens, on the web at http://blaster.docking.org. DOCK Blaster was developed in the Shoichet Lab at UCSF during the years 2000-2009. The service became public in August 2009, and a paper was published in J Med Chem in September 2009. The current version is 1.0.1.

What you need to start

To use DOCK Blaster you will need the structure of a protein target and an indication of the binding site. There are three ways to do this:

- If your target is in the PDB, you may simply specify the PDB code, in the Parser.
- If your target is not in the PDB, or you edited a PDB file, use the Preparer. The steps are:
  - Upload the target in PDB format (preferred) or mol2 format
  - Specify the binding site using
  - a docked ligand in mol2 format (preferred) or
  - "hot spots", in PDB format
  - atoms of residues forming the binding site, the center of inertia of which should be where you expect the ligand to go.
  - Click "DOCK" and wait for the job to run (typically under 1 hour).
- If you do not have a particular target in mind and are simply curious about DOCK Blaster, you may select "I'm feeling lucky", and we will pick a target for you from the PDB.

To try one of the examples featured in the DOCK Blaster paper.

Visualization Tools

UCSF Chimera (Chimera)

Chimera is developed by the Resource for Biocomputing, Visualization, and Informatics (RBVI) at the University of California, San Francisco, a program for interactive visualization and analysis of molecular structures. It helps us to obtain the structure either directly from the PDB

site or through many other formats, to localize the ligand that is in the active site and display the structure which is protein with the inhibitor. Secondary structure identification can be done, as it can show and hide ribbons. The secondary structure can observe motifs of the protein and also create a molecular surface around the protein, then color the surface according to different properties of the amino acids. Studying the protein-ligand interaction can be done by identifying the residues within 5.0A, and then identify the residues involved in the binding and label the residue names and types. Chimera shows the hydrogen bonds interaction between proteins and ligand.

RESULTS AND DISCUSSION

The medicinal properties of plants are due to the presence of active principles. These bioactive secondary metabolites are synthesized by two principal pathways: shikimic acid or aromatic amino acid, and mevalonic acid. Alkaloids, phenolics and terpenoids constitute many pharmacologically active compounds. Antioxidants are vital substances which possess the ability to protect the body from damage caused by free radical induced oxidative stress. Epidemiological studies specify that intake of fruits and vegetables have the ability to inhibit the damaging behavior of free radicals in the human body.

In our former present study the methanolic extracts were evaluated for phytochemical composition, total Phenolic content, flavonoid content, antioxidant potential by Total antioxidant assay, Reducing activity assays, Super oxide and hydroxyl scavenging activity, H2O2 decomposition assay. Efforts were also made to study on Thin layer Chromatography , HPLC finger printing, Lipid peroxidation, Antimicrobial Activity and Anti-tumor activity. Methanolic extracts of two traditionally used Indian medicinal plants namely *Elettaria cardamomum* and *Ferula assa-foetida* were selected for the study. Phytochemical analysis of plant extracts indicated the presence of major phytoconstituents, including phenolics, alkaloids, flavonoids, and saponin. Total phenolic content (1.71 mg/ml and 1.40 mg/ml expressed as gallic acid equivalents) was observed in *Elettaria cardamomum* and *Ferula assa-foetida* repectively. Antioxidant activity was measured by Phosphomolybdenum method. Free radical scavenging activity was evaluated using Superoxide anion scavenging activity , Hydroxyl scavenging activity and Hydrogen peroxide decomposition. The extract of *Elettaria cardamomum and Ferula assa-foetida* showed total antioxidant capacity and it was *25.60 mg/ml* and *18.43 mg/ml* calculated as Ascorbic acid equivalents respectively. Both the extracts exhibited the higher Reducing activity. The higher scavenging activity was observed in Ferula assa-foetida (82.55%)

as compared with Elettaria cardamomum (54.0%). Mild hydrogen peroxide decomposition has been observed in both the plants having 9.83 % and 9.60 % in *Ferula assa-foetida* and *Elettaria cardamomum* respectively. The *Elettaria cardamomum* and *Ferula assa-foetida* extracts showed concentration dependent hydroxyl radical scavenging activity and both plants Elettaria cardamomum and Ferula assa-foetida showing 33.94 % and 44.95 % respectively. The present finding strongly suggests that the use of *E.Cardamom and F. Asafoetida* extracts prevent LP leading to membrane damage consequent to radiation and to certain chemicals which generate potent ROS.

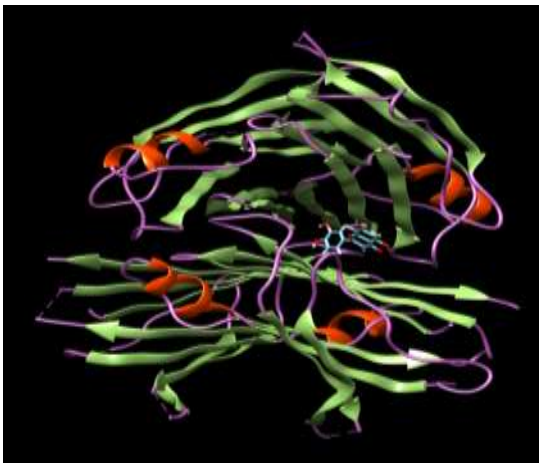

Figure 1: Docking of Luteolin-ligand & TTR (biomarker)-receptor

Total of 7 pockets were available to pick . Each picked pocket will be launched as a separate new DOCK Blaster job with a new job id

ii) VANILLIN DOCKING

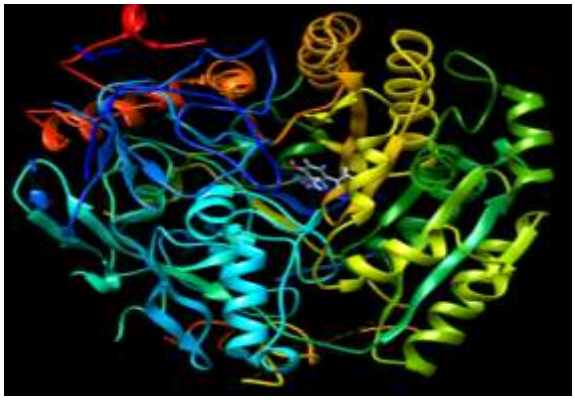

Figure 2: Vanillin dock with ligand FAD

Total of 13 pockets were available to pick. Each picked pocket will be launched as a separate new DOCK Blaster job with a new job id.

The results of one-dimensional TLC analyses show that different phenolic compounds, flavonoids and phenolic acids, are present in the investigated extracts. A largest number of

flavonoids (rutin, quercetin and some unidetified flavonoid-glycosides) and phenolic acids (chlorogenic, caffeic, coumaric and vanillic acid) was found in methanol extract. Rutin and some unidentified flavonoid-glycosides are present in the Solvent used : Chloroform: Ethyl acetate: Formic acid Ratio - (10:9:2) The extracts also contain coumaric, caffeic and chlorogenic acid when second solvent Methanol : Chloroform Ratio-(5:1) was used. Iodine balls vapour served as spraying method.

Three spots have been observed. 1st- Brown , 2nd- Yellow and 3rd- Green . The HPLC analysis showed that the extracts of *Elettaria cardamomum* and *Ferula assa-foetida* plant contain various secondary metabolites. The concentration of the various secondary metabolites present in the extracts ware determined based on the standard HPLC graphs. The standards used for analysis were tannic acid, vanillin and cathechol.

Furthermore, my study showed that the extract exhibited good antioxidant activity with a high content of polyphenol and flavonoid compounds in lipid peroxidation assay. These findings indicate that the potent antioxidant activity *of E. Cardamomum* and *F. Assa-foetida* extract partly contributes to the amount of polyphenol and flavonoid compounds.

In addition Methanoic extract of *Elettaria cardamomum* and *Ferula assa-foetida* revealed anti microbial and effective anti-tumor activity. We have also carried out Molecular DOCKING with the help of DOCK BLASTER- An Online tool for docking and it provided us with molecules having least energy level ranging -24 k/cal/mol to -31 k/cal/mol (phytochemicals as proteins ligands and receptors asscociated with different Cancers.) that could have anti cancerous activity.

MOLECULAR DOCKING:

In order to find suitable ligand for selected phytochemicals we have searched ligands and super ligands from Protein Data Bank which are directly related to either Cancer proliferation or Tumor as discussed in table 2.

Table 1: Subclasses and Dietary Sources of Flavonoids

Flavonoid subgroup	Representative flavonoids	Major food sources
Flavonols	Kaempherol,myricetin, quercetin, rutin	Onions, cherries, apples, broccoli, kale, tomato, berries, tea, redwine, tartary buckwheat
Flavanols	Catechin, gallocatechin	Apples, tea
Isoflavones	Daidzein, genistein, glycitein, formononetin	Soya beans, legumes
Flavanones	Eriodictyol, hesperitin, naringenin	Oranges, grapefruit
Flavanonols	Taxifolin	Limon, aurantium
Flavones	Apigenin, chrysin, luteolin	Parsley, thyme

Table 2: Phytochemicals as ligands and cancer molecules as receptors:

S.NO	Ligand	PDB ID	Details	Receptor	Associated cancer type	Energy level (kcal/mol)
1	Luteolin	LU2	Mwt: 286.239, xLogP: 1.97 Charge: 0, RotBond: 1 # Protomers: 1, Contact: 4 ES: -11.43 VdW: -18.46 Desolv: p=5.38, ap=0.70 Formula : $C_{15}H_{10}O_6$ Molecular weight: 286.24 g/mol	TTR (biomarker)	ovarian	-23.80
				Tankyrase	telomerase directed cancer eg HeLa cancer cells, ovarian cancer	-38.31
				PPAR gamma ligand	Lung cancer	-25.45
2	Vanillin	FAD	Mwt: 343.217, xLogP: 2.92 Charge: 0, RotBond: 1 # Protomers: 2, Contact: 2 ES: -7.91 VdW: -26.80 Desolv: p=6.15, ap= - 3.1		Colorectal cancer	-31.65
3	(±)-α-Pinene Alpha pinene	1MPW	**ID:** 6402, **Molecular Formula:** $C_{10}H_{16}$ Average mass: 136.234 Da Monoisotopic mass: 136.125198 Da	Human Cytochrome P450 Enzymes	neuroblastoma cells, breast cancer	-37.56

4	Ferulic Acid	FER	Formula: C10 H10O4 Number of non-H atoms: 14 Number of rotable bonds: 3 Structure derived from PDBID:1KYZ	S-adenosyl-L-Homocysteine (DNA Methylation)	Liver Kidney brain	-52.21
5	Quercitine	1JUH	Classification: Oxidoreductase Structure Weight: 160107.39 Formula C15 H10 O7 Molecular Weight 302.24 g/mol Type non-polymer	Beta-D-Mannose	breast, colon, prostate, ovarian, endometrial, and lung tumors	-51.36
				Protein kinase (PK)	hematologic malignancies B cell lymphoma	-43.27
6	Indole 3 Carbazol		Formula: C_5 H_{11} N O_2 Se Molecular Weight:196.11 g/mo	Selenomethionine	*proliferation* of hepatocellular, pancreatic, and colon *carcinoma*	-47.78

CONCLUSION

The tested plant extracts showed promising antioxidant and free radical scavenging activity, thus justifying their traditional use. Additionally we have evaluated Pharmacognostic study, Physicochemical analysis, Phytochemical study, *In vitro* antioxidant activity, TLC and HPLC analysis, Lipid peroxidation, In vitro anti-microbial activity, Antitumor activity and last Molecular docking of selected phytocontituents having anti tumor properties of both plants with DOCK BLASTER-ONLINE software in order to create anti tumor or anti cancerous drug.

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