An innovative solution for the treatment of pancreatic cancer by Using Ginger and Peppermint

Harapriya Sahoo

Department of Biotechnology,

Centurion University of Technology and Management, Bhubaneswar

ABSTRACT

Review of the paper shows the effectiveness of Ginger (Spice) & Peppermint (Medicinal plant) for better treatment of pancreatic cancer. Cancer is a complex set of diseases and is one of the most devastating diseases worldwide. Pancreatic adenocarcinoma is a low-incident but highly mortal disease. It accounts for only 3% of estimated new cancer cases each year but is currently the fourth common cause of cancer mortality. By 2030, it is expected to be the 2nd leading cause of cancer death. Medicinal plant and spices have been used for generations by humans as food supplements and to treat some ailments. Surgery, chemotherapy which have no guarrenty to live a long time due to their antioxidant property. so I took the Pappermint, ginger which have Medicinal properties & anti-cancer activity. Docking between the gene of pancreatic cancer and phytochemicals of the spice & medicinal plant which provide significant protection against cancer.

Key words: Adenocarcinoma, Chemotherapy, Surgery, Antioxidant, Phytochemicals, Anti-cancer activity

1. INTRODUCTION

Pancreatic cancer

Pancreatic cancer is a cancer when abnormal cells begin to grow within the pancreas, which is also a genetic disease caused by mutation in DNA. It has been called a 'silent' disease because early pancreatic cancer usually does not cause symptoms. If the cell mass blocks the common bile duct, and bile cannot pass into the digestive system, the skin and whites of the eyes may become yellow (jaundiced), and the urine may become darker as a result of accumulated bile pigment (bilurubin).

Out of 1750 genes I selected TP53, which is located in chromosome no.-17.

How pancreatic cancer occurs ?

Pancreatic cancer occurs when cells in your pancreas develop mutations in their DNA. These mutations cause cells to grow uncontrollably and to continue living after normal cells would die. Untreated pancreatic cancer spreads to nearby organs and blood vessels. Most pancreatic cancer begins in the cells that line the ducts of the pancreas. Cancer can also form in the hormone-producing cells or the neuroendocrine cells of the pancreas.

Rarely, there can be familial or hereditary genetic syndromes arising from genetic mutations that run in families and put individuals at higher risk, such as BRCA-2 and, to a lesser extent, BRCA-1 gene mutations.

Risk factors: A risk factor is anything that increases a person's chance of developing cancer. A person with an average risk of pancreatic cancer has about a 1% chance of developing the disease. Generally, most pancreatic cancers (about 90%) are considered sporadic. Also called somatic mutations, this means the genetic changes develop by chance after a person is born. There is no risk of passing these genetic changes on to one's children. Inherited pancreatic cancers are less common (about 10%). They occur when gene mutations or changes are passed within a family from one generation to the next. These are also called germ-line mutations. Due to smoking, diabetes mellitus, chronic pancreatitis, gender, obesity, diet, age, race/ethnicity, there is a chance to lead cancer.

Types: It is classified into two main types, those forms in the exocrine gland and endocrine gland. About 95% of pancreatic cancers begin in the exocrine (enzyme-producing) cells of the pancreas.

Exocrine cancer- Most cancer affecting the exocrine gland are called adenocarcinomas. This type of cancer forms in the pancreas ducts. Treatment for these cancers is based on stage of growth.

Endocrine cancer- These cancers are less common and are most often benign. Rarely cancer stemming from a pancreatic endocrine tumor (PET) affects the hormone-producing cells. These tumors are also called islet cell tumors or neuroendocrine tumors.

Symptoms: Pain in the upper abdomen, Loss of appetite, Depression, Diabetes, Blood clots, Fatigue, Yellowing of your skin and the whites of your eyes (jaundice).

Clinical scenarios detected by molecular & Histopathological features of pancreatic cancer:

Immune Phenotypes	Mutational profile	Clinicopathologic Features
Immune Escape Rich in immunosuppressive T-cell & myeloid cell population	KRAS, TP53. CDKN2A, SMAD4, PLK3CA	High-grade tumor budding Poor outcome
Immune Rich Rich in cytotoxic T-cell populations. Presence of TLTs	KRAS, TP53, STK11, SMARCB1	Infrequent tumor budding Better outcome
Immune Exhausted High PD-L1 expresssion inflamed TME, rich in cytotoxic & immunosuppressive T-cells	KRAS, TP53,PLK3CA, JAK3	Frequently high grade tumor budding Very poor outcome

Ginger (Spice)

Scientific name -*Zingiber officinale*

Family – Zingiberaceae

Chemical analysis of ginger shows that it contains over 400 different compounds. The major constituents are carbohydrates (50–70%), lipids (3–8%), terpenes, and phenolic compounds . Terpene components of ginger include zingiberene, β-bisabolene, α-farnesene and α-curcumene, while phenolic compounds include gingerol, paradols, and shogaol. These gingerols (23–25%) and shogaol (18–25%) are found in higher quantity than others.

Besides these, amino acids, raw fiber, ash, protein, phytosterols, nicotinic acid, vitamin A, and minerals are also present. Experimental studies showed that ginger and its active components including 6- gingerol and 6-shogaol exert anticancer activities against GI cancer.

Anti-cancer & anti-inflammatory effects:

Ginger and its products raise the immune system. It is giving the anti cancer effect against the pancreatic cancer. Phytochemicals like gingerol, shogaol, paradol, and zerumbone in ginger exhibits anti-inflammatory and antitumorigenic activities. Ginger and its bioactive molecules are effective in controlling the extent of colorectal, gastric, ovarian, liver, skin, breast, and prostate cancers. They can also inhibit synthesis of pro-inflammatory cytokines such as IL-1, TNF-α, and IL-8.

Peppermint (Medicinal plant)

Scientific name – *Mentha Piperita*

Family – Labiatae

It is a hybrid mint, a cross between Watermint and spearmint. Peppermint has a high Methanol content. The oil also contains menthone and carboxyl esters, particularly menthyl acetate. Dried peppermint typically has 0.3–0.4% of volatile oil containing menthol (7–48%), menthone (20–46%), menthyl acetate (3–10%), menthofuran (1–17%) and 1,8-cineol (3–6%). Peppermint oil also contains small amounts of many additional compounds including limonene, pulegone, caryophyllene and pinene. It contains terpenoids and flavonoids such as eriocitrin, hesperidind and kaempferol 7-O- rutinoside.

Anti-cancer & anti-inflammatory effects:

The chemical composition, anti-inflammatory, cytotoxic and antioxidant activities are assessed against human cancer cells. Most importantly peppermint facilitates digestion and it does this by stimulating the secretion of bile and digestive juices. Its actions include carminative (anti-gas), anti-inflammatory, anti-spasmodic, anti-emetic (anti-vomiting), nervine (sooths the nerves), anti-microbial, and last but not least analgesic, or pain killing. Peppermint has a great anti-oxidant, anti-cancer & anti inflammatory activities in pancreatic cancer.

2. MATERIALS AND METHODOLOGY

Required materials

a) Molegro virtual docker 4.0.2 software:

It is an integrated environment for studying and predicting how ligands interact with macromolecules. The identification of ligand binding modes is done by iteratively evaluating a number of candidate solutions (ligand conformations) and estimating the energy of their interactions with the macromolecule. The highest scoring solutions are returned for further analysis. MVD requires a three-dimensional structure of both protein and ligand (usually derived from X-ray/NMR experiments or homology modeling). MVD performs flexible ligand docking, so the optimal geometry of the ligand will be determined during the docking.

b) NCBI Website:

(https://www.ncbi.nlm.nih.gov)

It is an online tool where major databases are included. We can search here for any database such

as genes, proteins, Pubmed, Taxonomy, Nucleotides, Biosamples etc.

c) PDB Website:
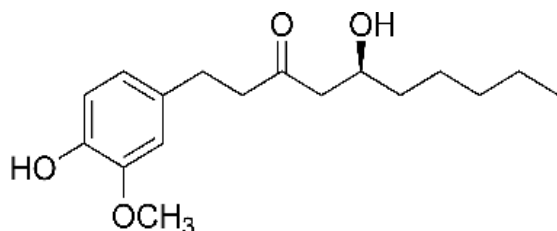
(https://www.rcsb.org)

The RCSB PDB builds upon the data by creating tools & resources for research, Education in Biotechnology field. We can achieve informations about the 3D shape of proteins, nucleic acids & complex assemblies.

d) TP53 gene:

It is a tumor suppressor gene which locates in the chromosome no-17 and provides instructions for making a protein called tumor protein p53 / p53 (53 is the weight of protein). When the DNA in a cell becomes damaged by agents such as toxic chemicals, radiation, or UV rays, this protein plays a critical role in determining whether the DNA will be repaired or undergo apoptosis. If the DNA can be repaired, p53 activates other genes to fix the damage. If the DNA cannot be repaired, this protein prevents the cell from dividing and signals it to undergo apoptosis. Because p53 is essential for regulating cell division and preventing tumor formation, it has been nicknamed the "guardian of the genome."

e) Gingerol :

It is the active constituent of fresh ginger which has positive effects in pancreatic cancer. Chemical structure-

f) Menthyl acetate :

It is an active pharmacophore of Peppermint which has anti cancer activity for the treatment of pancreatic cancer. Chemical formula- $C_{12}H_{22}O_2$, PubChem CID: 220674
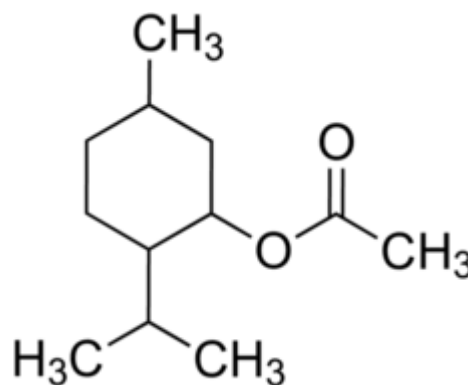
Procedure

Step-1: Go to NCBI homepage, select the database gene, search the name of particular cancer, take your desired gene.
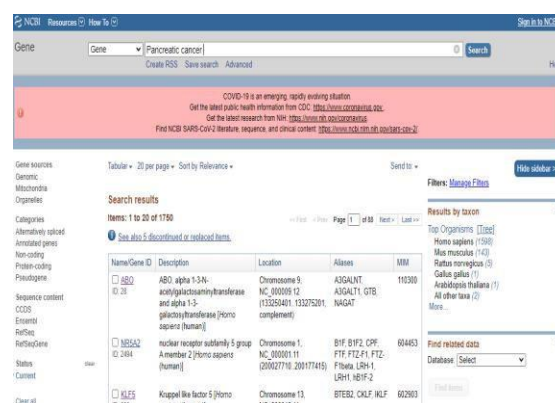
Step-2: Go to PDB homepage, search the selected gene, pharmacophores of spice & medicinal plant which you have selected and download the PDB formats respectively in your own choice.

Step-3:To import file in MVD

1. Open the Molegro Virtual Docker 4.0.2software. If the workspace is not empty, we will start by clearing it (select File | Clear Workspace).

2. Then we will add some structures. This can be done by selecting (File | Import Molecules).

3. Start by importing the file from the desktop and this file is an unmodified file taken from the RCSB Protein Data Bank.

Step-4: Choosing molecules to import

1. First we imported the protein.

2. Deselect the water, ligand & cofactors.
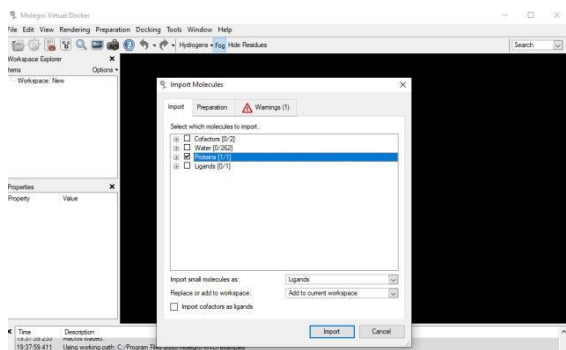
Step- 5: Choosing preparation type

1. Select the Preparation tab.

2. Some structures contain information about bond types and bond orders, and have explicit hydrogens assigned. However, PDB files often have poor or missing assignment of explicit hydrogens, and the PDB file format cannot accommodate bond order information.

3. Then Assign All Below to Always. This ensures that all preparation will be done by MVD.

4. If the protein structure has been prepared beforehand and saved in a format capable of handling all structural information (e.g. Mol2 file format), we should import it via the default preparation setting If Missing.

5. This setting only performs a given preparation if the required information cannot be found in the file.
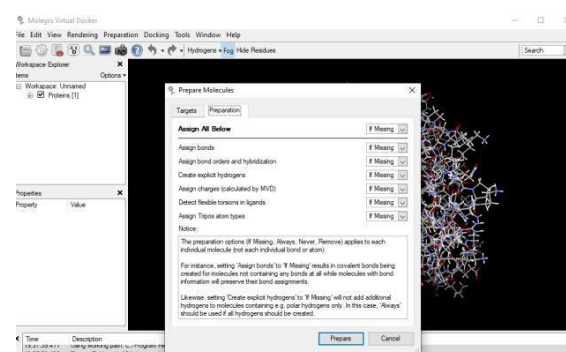

Step-6: Inspecting the warning

1. The last tab in the import dialog (Warnings (1)) shows potential problems with the structure file.2. Then click the Import button. The protein appears .
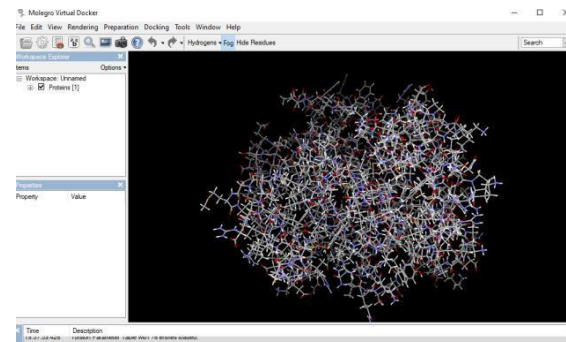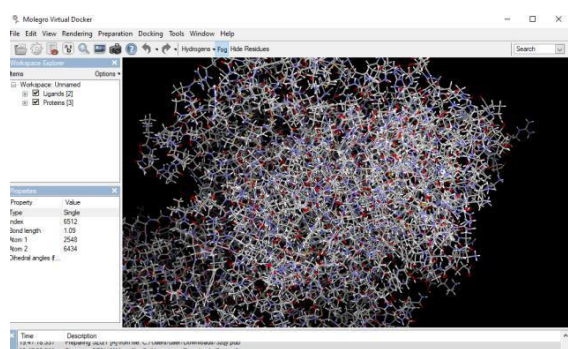

Step-7: Import ligand molecule

1. Import the ligand molecule.

2. Deselect the water. The import dialog shows two proteins: actually these are two chains from the same protein. It also indicates that a ligand has been detected in the PDB file

3. Then in visualisation window it will apper like this-
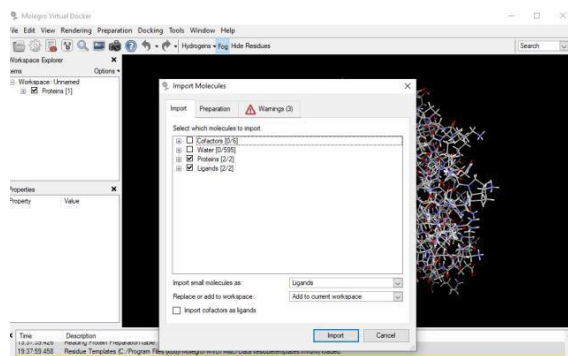
Now we can see the protein ligand binding.

Step-8: Docking

1. Here the Errors and Warnings tab in the Docking Wizard shows potential problems with the docking setup (if any). It should not show any warnings at this stage.

2. Press the Next button to proceed to the last tab.

3. In the Setup Docking Execution tab , several choices are available for executing the docking simulation. We will use the default settings

4. Finally, the Output directory specifies where the docking data (log file and found poses) will be stored.

5. Now we will begin the docking simulation by pressing the Start button.

6. The MVD Batch job dialog appears showing the docking progress.

7. While the simulation is running the energy of the currently best found pose (the pose with the lowest energy) can be observed on the Graph tab page. The graph shows the docking score (in arbitrary units) as

a function of number of iterations performed by the docking search algorithm.
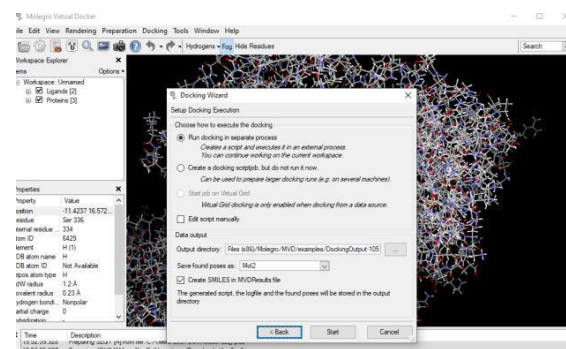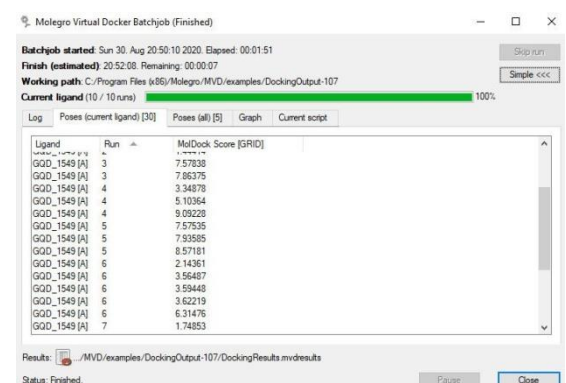

Step-9: Outcome result

1. Another tab will display where molegro virtual docker batch job will be finished.

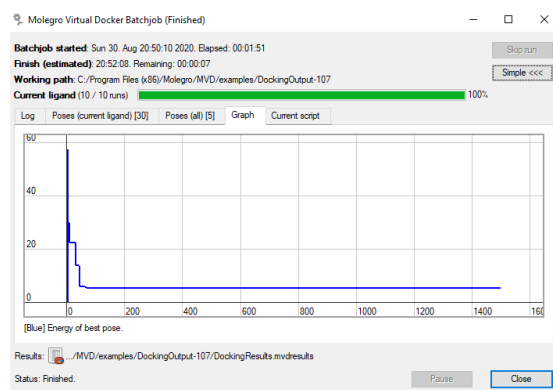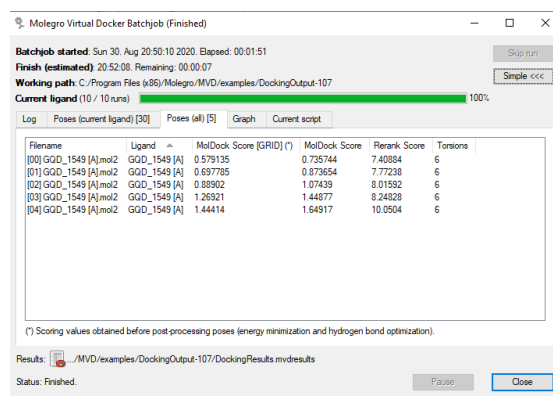2. it will appear like this on the desktop screen.
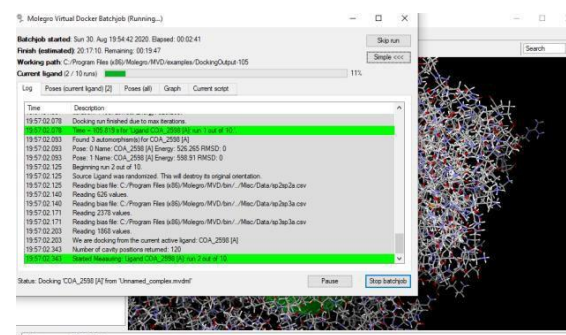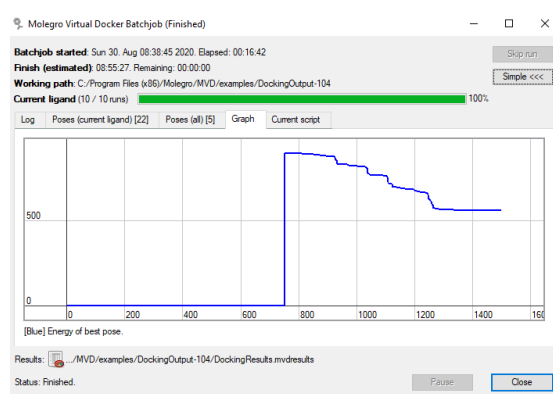

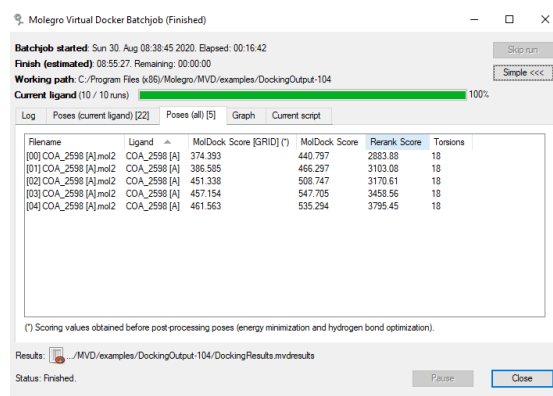3. Then we can get mol dock score & graph.

RESULT

Docking of 5ZQY (PDB format of TP53 gene) with 5FQP (PDB format of gingerol, chemical constituent of Ginger).

Docking of 5ZQY (PDB format of TP53) with 4EU6 (PDB format of Menthyl acetate, ingradients of Peppermint).

3. CONCLUSION

It has concluded that we can cure pancreatic cancer by the invension of medicine using the chemical constituents of ginger & Peppermint because it gives positive result when docking takes place between the protein of Menthyl acetate of Peppermint (4EU6) with the protein of the gene TP53 (5ZQY) and the protein of Gingerol (5FQP) with 5ZQY of Pancreatic cancer. cancer by invention of new medicines. This data indicates that these constituents accumulate in the gastrointestinal tract, which supports the many observations of effectiveness as an antinausea agent and as a possible pancreatic cancer-preventing compound.

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