Docking Studies on Breast Cancer Genes (BRCA1) With Tea Components

Noopur Khare, Jibu Thomas

***Abstract*— Cancer is the life threatening disease today. Among the different types of cancer Breast cancer is the most prevalent disease leading to the death of women every year. Mutation or alteration in gene is responsible to cause breast cancer. BRCA1 is known as Breast cancer susceptibility gene 1 act as a concierge for DNA which confirms its stability, maintain the integrity. Mutation in BRCA1 gene leads to generate truncated protein which is responsible for heritable breast cancer. Considering the increasing epidemic severity of breast cancer, this present study has focussed on designing, analysis of potential inhibitor by tea polyphenols with the help of molecular docking tool which can bard the function of abnormal protein. In the present venture docking studies reveal that epicatecin-3-gallate is having the least minimization energy of -35233599 and docking score with -50878989. Thus, the results proves that the ligand, epicatecatechin -3-gallate can be use as potent inhibitor.**

***Index Terms*— Cancer, BRCA1, epicatecatechin**

I. INTRODUCTION

Cancer is a disease where cells start growing in an abnormal way. Sometimes it is caused by manipulation in gene or gene expression. Normally cells divide, grow and died but in cancerous condition cells divide and re divide which are responsible for more mutation. This mutated gene also passes from one generation to another.

Breast cancer originates from the tissue of breast, where cells in breast grow without control. Generally it begin in two parts i.e. lobule, which is a milk producing glands, ducts which connects lobule to nipple. Reason for breast cancer is still unknown but factors like late pregnancy, early menstruation, late menopause [8], race, older age [1], lack of breast feeding , less children [25] hormone therapies , mutation in genes influence the growth of tumour.

Paul Broca was the first person to interpret a family with high risk of breast cancer. His wife suffered from breast cancer , when he generate progeny of his family he estimated that four generation could be suffer from same [2]. This finds that breast cancer is a heritable disease. BRAC1 gene was discovered in 1990. BRAC1 is cited on 17q b, 21, contain 38530994 base pair ([4],[6]). Women who is a carrier of BRCA1 is not only having risk of developing breast cancer but also having a risk of developing fallopian tube, ovarian, prostate and pancreatic cancer [9]. The gene contains 24 exons, its coding region start from middle of exon [12]. It encode large no of proteins. It consists of 1863 amino acids.

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In BRAC1 gene, exon 1 is non coding and exon 11 is very large [19]. It has highly rich zinc binding RING finger domain which code for protein known as E3 ligase that help i ubiquitination [11] , if mutation occur in this zinc finger domain it inactivate the E3 ligase , hence inactivate the function of BRAC1[16]. It has another domain known as BRCT domain. This gene is expressed in a number of tissues and also in breast [15].

Studies proved that deletions, insertions, non sense mutations, splicing aberration are the main reasons for the pathogenic mutation of BRCA1 gene that result in the generation of truncated protein [3].

BRCA1 helps to repair the damaged DNA or it destroys cells if DNA cannot be repaired. BRCA1 is identified as p53 interacting protein [26], also interact with RAD 51, a protein that has been involve in repairing mechanism and DNA recombination [20].RAD 51 is the major component in DNA repairing process. BRAC1 forms complex, which will further initiate the repairing of double stand breaks. BASC is known a BRAC1 associated genome surveillance complex comprises of many other tumour suppressor gene such as ATM, MLHI MSH6 etc they together involve in the DNA repairing process[24].If by chance the damage occur to BRCA1 then it cannot repair the damaged DNA , hence increase the risk of developing tumour [5].

According to Breast cancer core database it has estimated, nearly 1,639 types of mutation and polymorphism in the BRAC1 gene. Defect or any mutation in BRAC1 leads to the development of cancer in women Breast cancer is 100 times more in women than men [13].

II. GREEN TEA FLAVNOLS AS TUMOR SUPPRESSOR

Different Phytochemicals compound in green vegetables and fruits having therapeutic properties. Nowadays an extensive research is being performed taken into the consideration of these plant compounds for drug discovery process. Different types of herbs play an important role in preventing and treating cancer disease. *Camillia sinensis* commonly known as green tea is second largest beverages consumed in worldwide next to water. Recent studies demonstrated that the polyphenols present in green tea act as antioxidant, hence having anticarcinogenic and antimutagenic activity. The major tea polyphenol are catechin, epigallocatechin, epicatechin-3-gallate, epigallocatechin-3-gallate. Stages of cell cycles are controlled by cyclic activation and inactivation of cyclin dependent kinases (CDKs) [22]. Different types of tumour suppressor protein monitor and control the DNA damage process. Inactivation of tumour cell, overexpresion of cyclins and CDKs initiate the cancer. Recent studies have demonstrated that tea

polyphenols arrest the cell cycle by controlling over the cyclin, CDKs and different tumor cells ([10],[18]).

In the present study array of tea flavanols were analysed which could trigger the activity of mutated BRCA1.

Table I
Different Tea Polyphenols

S No	Tea polyphenols
1	Catechin
2	Epicatechin
3	Epicatechin-3-gallate
4	Epigallocatechin
5	Catechin
6	Epigallocatechin-3-gallate
7	Theaflavin
8	Caffine

III. MATERIALS AND METHODS

A. *Docking software: Schrodinger*

Schrodinger is highly paid software. It works on the maestro interface. It is very flexible, user friendly software used for homology modelling, molecular docking and drug designing.

B. *Protein structure*

The structure of BRCA1 (ID: 3PXB) is retrieved from PDB (Protein Data bank) and its ribbon structure was generated by Schrodinger in mol format.

C. *Active site determination*

Active site is determined by CASTp. Three larger pockets or active sites were selected. There amino acid residues are: isoleucine, glutamic acid, leucine, glycine, tryptophan, lysine, phenyl alanine ,threonine , valine , proline ,alanine , tyrosine.

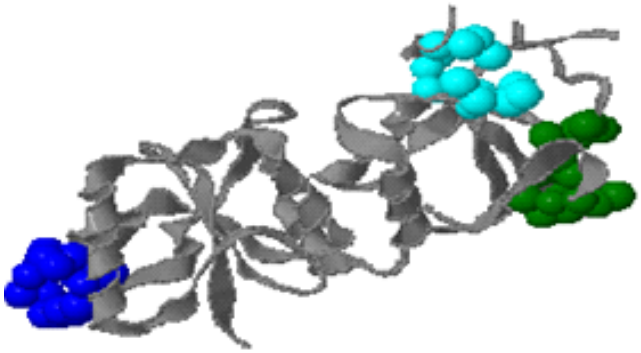

Figure 1: Active Sites in BRAC1

D. *Ligand collection and verification*

Ligand is defined as any component that binds with the receptor. Ligand collection was done by Pubchem. The mol structures of different ligands- catechin, epicatechin-3-gallate, epigallocatechin-3-gallate, epicatechin, epigallocatechin were generated by Schrodinger.

The validations of structures are done by Moleinspiration to check the bioactivity of selected ligands. It is an online tool.

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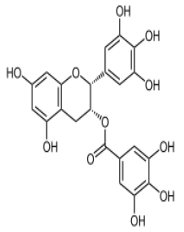
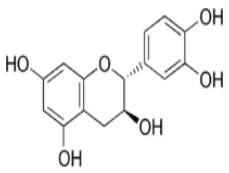
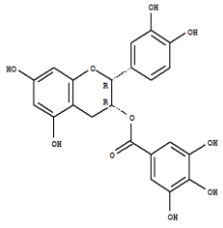


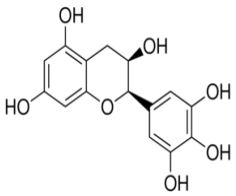
Epigalloctechin gallate



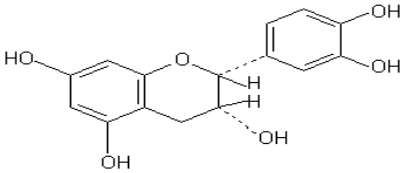
Catechin



Epicatechin -3 -gallate



Epigallocatechin



Epicatechin

Fig:2 Green Tea Polyphenols

E. *Protein preparation in schrodinger*

The protein preparation is done by Schrodinger to make the structure stable.

F. Grid generation

Grid generation is done using glide software. An area in the protein which is more applicable for docking is shown by grid. Basically it is used to make the area rigid in protein for docking in a given axis.

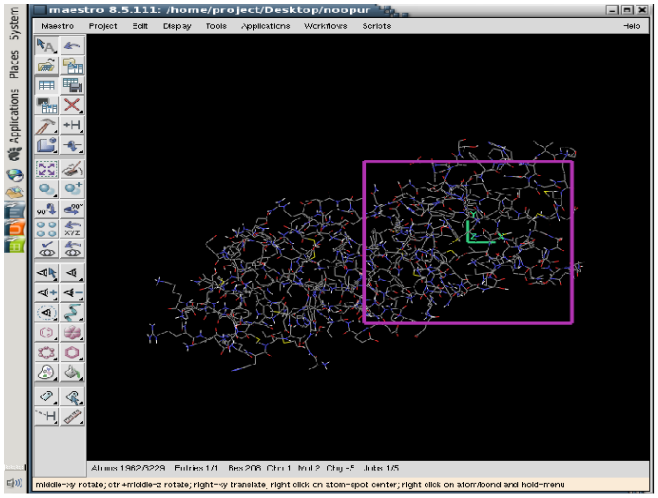


Fig:3 Grid Generation

G. Docking results

The Docking were done by Schrodinger Software in three step HTVS, SP, XP.

H. Glide energy and score

Three levels of docking- XP, SP, HTVS were analysed. The molecule having the least energy and least docking score is selected as it is more stable. The current research focused on docking of cancer protein, BRCA1 with array of tea components i.e., catechin, epicatechin, epicatechin-3-gallate, epigallocatechin , epigallocatechin -3-gallate.The results were described on the basis of energy minimization and docking score. The molecule having the least energy and least docking score can be selected as an inhibitor as it will be more stable. In the present research Docking studies demonstrate that epicatechin-3-gallate is having the least energy of -35233599, docking score of -50878989. Thus, the results proves that the ligand, epicatecatechin -3-gallate can be selected as an inhibitor.

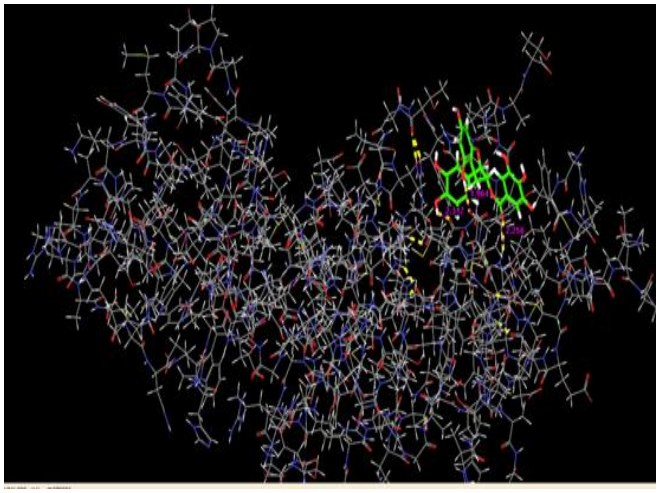


Fig: 4 Showing Docking- Hydrogen bonds and neighbouring residues.

Table II
Showing glide energy, XP score, Docking core and Acceptor / Donor Residues

Pubchem ID	**Glide energy**	**XP score**	**Glide score**	**Docking score**	**Donor/ acceptor**
Epicatechin 3 gallate	-35233599	-5087898	-5087898	-5087898 9	2
Catechin	-27609818	-45687 2	-456872	-456872	1,1
Epicatechin	-28867071	-28533 85	-285338 5	-2853385	2,1

Table III
Amino acid involved at binding sites

Amino acid involved at binding sites
LYS 1793, LYS 1793, PHE 1772, VAL 1838, VAL 1736,VAL 1784, GLU 1794, VAL 1842

IV. DISCUSSION

Recent studies have shown any type of mutation of the BRCA1 gene, resulted in the generation of mutated BRCA1 protein [3] which is a hallmark of breast cancer. Ligand Protein docking is key tool in drug discovery process. Docking is a novel method in which the ligand, binds on the pockets or active site of the receptor molecule. This method is regarded as one of the major innovation in drug discovery. This present study is about docking of mutated cancer protein with different polyphenols of tea. Green tea is having anticarcinogenic and antimutagenic activity, therefore it is more efficient ligand, to inhibit or suppress the activity of mutated BRCA1. The results are demonstrated on the basis of least energy and least docking score Molecules having the least energy will be regarded as more stable. On the basis of XP, SP, HTVS it was found that epicatechin-3-gallate is having the least energy; hence it's more efficient and capable of blocking oncoprotein responsible for breast cancer.

V. CONCLUSION AND SUGGESTION FOR FURTHER RESEARCH

Green tea is an important medicinal plant. Tea polyphenol compounds are having tumour suppressor properties. Polyphenols act as antioxidants and can neutralise free radicals, it reduces or suppress the activity of cancer cells. These compounds are eco-friendly and have fewer side effects. Green tea catechin plays an important role in arresting

abnormal cell growth or inducing apoptosis The results obtained from this study would be useful in both understanding the triggering effect of tea compounds as well as prove useful in further drug discovery process. The results are demonstrated on the basis of energy and docking score. The least energy molecule can be selected as an inhibitor. From the present study it is concluded that epicatechin-3-gallate can be used as an inhibitor in future. Still some research has to be carried out especially *invivo* for the validation to ensure the activity of ligand and triggering mechanism of oncoprotein and also to determine different dosage levels order to give the promise approach for controlling of this deadly disease.

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