In silico analysis of Phytochemicals to Treat Estrogen positive Breast Cancer

Drushti H. Bhatt[1], Himanshu A. Pandya[1] And Yogesh T. Jasarai[1]

[1] *Department of Bioinformatics, Applied Botany Centre, Gujarat University, Ahmedabad - 380 009, Gujarat, India.*
[*] *Corresponding Author : drushtibhatt@yahoo.com*

ABSTRACT

Estrogen is the imperative factor that has implications in breast cancer. The over expression or activation of estrogen occur frequently in breast, ovarian and lung cancer prove them an important therapeutic target for breast cancer studies. Hormone therapy was focused for detailed analysis for estrogen positive breast cancer. The presence of dietary agents was evident and identified from fruits and vegetables source, can act on estrogen positive breast cancer and can be potentially used as therapeutic drug based on their affinity toward target receptor in this therapy. Molegro Virtual Docker tool was used for analysis of binding energy and hydrogen binding etc. The promising effects of phytochemicals present in dietary products on breast cancer could be determined.

Keywords: Estrogen, Estrogen receptor, Hormone therapy, Phytochemicals, Molegro Virtual Docker

INTRODUCTION

Breast cancer is the most common type of diagnosed cancers and the second major cause of death among women in Occidental countries. Large majorities of breast cancers are sporadic but up to 10% can be attributed to genetic predisposition. Breast cancer cells can spread by breaking away from the original tumor. They enter blood vessels or lymph vessels, which branch into all the tissues of the body. The cancer cells may be found in lymph nodes near the breast. The cancer cells may attach to other tissues and grow to form new tumors that may damage those tissues.

Hormones exist naturally in the body. They help to control how cells grow and what they do in the body. Hormones, particularly estrogen, can encourage some breast cancer cells to grow.Hormonal therapy medicines treat hormone-receptor-positive breast cancers in two ways: 1). by lowering the amount of the hormone estrogen in the body 2). by blocking the action of estrogen on breast cancer cells. Estrogen makes hormone-receptor-positive breast cancers grow. So reducing the amount of estrogen or blocking its action can reduce the risk of early-stage hormone-receptor-positive breast cancers coming back (recurring) after surgery.

Hormonal therapy medicines can also be used to help shrink or slow the growth of advancedstage or metastatic hormone-receptor-positive breast cancers. Hormonal therapy medicines are not effective against hormone-receptor-negative breast cancers. There are several types of hormonal therapy medicines, including aromatase inhibitors, selective estrogen receptor modulators, and estrogen receptor downregulators. Before and after menopause, the patient may be offered hormone

therapy with tamoxifen, it behaves as an agonist/antagonist. The tamoxifen competes with estrogen to bind with estrogen receptor and restrict the change in shape of receptor, which further binds to coactivators.being paid to the possibility of applying cancer chemopreventive es, - tumor properties and have provided ntified from -carbinol (apples, black and green tea, biloba leaves,widely , Ginsenoside (Ginseng plant) etc. micals) from PubChem and docked with shape of receptor, which further binds to coactivators.

Increasing attention is agents for individuals at high risk of neoplastic development. For this purpose by natural compounds have practical advantages with regard to availability, suitability for oral application, regulatory approval and mechanisms of action. Candidate substances such as phytochemicals present in foods and their derivatives have been identified by a combination of epidemiological and experimental studies. Plant constituents include vitamin derivativ phenolic and flavonoid agents, organic sulfur compounds, isothiocyanates, curcumins, fatty acids and d-limonene. Phytochemicals have potent anti multiple active compounds in the past.

Although there is an increasing focus on designer therapeutic anticancer agents, the broad spectrum of activity of natural products across multiple signalling pathways remains inadequately explored. Here, we briefly present evidence that dietary agents ide fruits and vegetables can act to modulate the effects of deregulated cell cycle checkpoints, and this may contribute to the prevention of cancer. The agents include Indole 3 (cruciferous vegetables), Theaflavin (tea leaves), Quercetin capers) and epigallocatechin-3-gallate (green tea), Ginkgetin (ginkgo cultivated tree), Hyperoside (Drosera rotundifolia)

We have taken eighteen natural ligands (phytoche estrogen receptor using Molegro Virtual Docker (MVD) tool

Computational method:

Several offline tools, online tools and databases were used to accomplish this work. The process was started by retrieving crystal structure of estrogens receptor (PDB ID: 1A52) from Protein Data Bank. Next, the eighteen natural compounds were derived from PubChem. This database contains substance database, compound database and BioAssay database. The library of ligands was obtained from Compound Pubchem. The detailed information like molecular weight, 2D and 3D structures, IUPAC name and H-donor/acceptor of compounds can be obtained from PubChem. Further, the interacting residues within the pocket of receptor had been identified by PDBSum. So, the probable binding site, which has been made between ligand and protein, number of residues of protein and type of proteins for docking the molecules can be known. Finally, Docking studies and Absorption**,**

Distribution**,** Metabolism**,** Excretion and Toxicity (ADMET) properties or drug likeliness of natural compounds and estrogen receptor (PDB ID: 1A52) were observed using MVD and FAF Drug2 respectively.

RESULT AND DISCUSSION

After docking, the natural compounds bind estrogen receptor same as Tamoxifin binds, which is

drug available in market to treat the breast cancer as of now. Tamoxifin and other compounds embedded within cavity of receptor and form hydrogen bonds at Arg 394, His 524 and Leu 525 position (Figure 1). The some of the ligands out of eighteen natural ligands require lower energy compare to Tamoxifin to form stable conformation (Table 1). Tamoxifin requires -117.917 Kcal/mol energy but Ginsenoside and Hyperoside require -140.071 Kcal/mol and -137.124 Kcal/mol respectively. And also found Epigallocatechin gallate and Ginkgetin require -135.747 Kcal/mol and -134.482 Kcal/mol respectively (Table 1).

Out of 18 compounds, there are 4 compounds, which showed lower energy. But before the use these compounds as therapeutics we have to check them in ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) properties. The *insilico* ADMET analysis qualifies the entire natural product fit as drug like molecule by FAF drug. From the result of the ADMET test of selected 4 compounds, which gives lower binding energy to targeted receptor, all these compounds comes in the normal range and qualifies as drug like molecule (Table 2). The different properties like Molecular weight, hydrogen donors and accepter, flexible and rigid bonds, ring number, ring size, carbon atoms, heavy atoms, number of charges and Log P values etc (Table 2). The out of 4 natural ligands, Ginsenoside has lower Molecular weight compare to others. It is near to Tamoxifin (Table 2).

Natural ligands

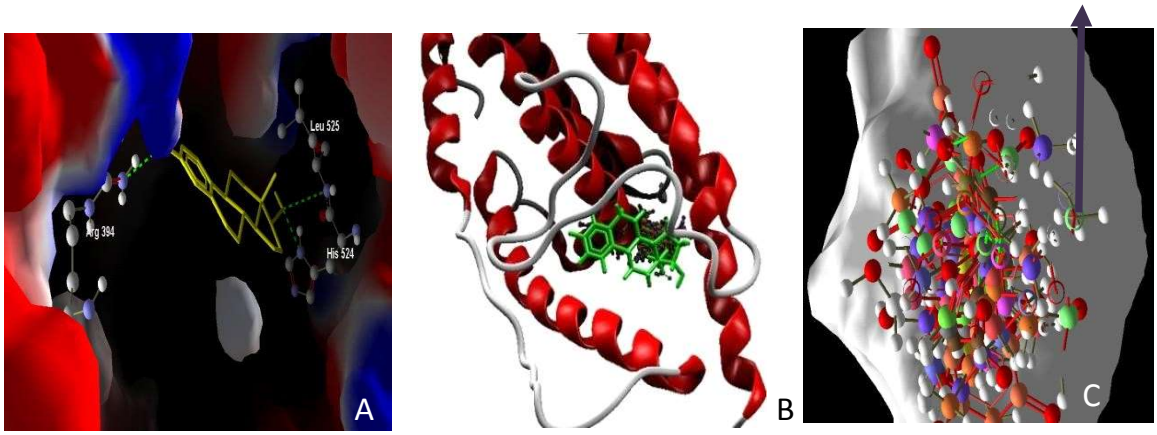

Fig-1 (A) The surface view of estrogen receptor forms hydrogen bonds with Tamoxifin at Arg 394, His 524 and Leu 525 position. Yellow color represent Tamoxifin, green dotted line presents hydrogen bond within surface environment. (B) Secondary structure of estrogen receptor with natural ligands and Tamoxifin. Red color represents helices of receptor and white color represents chains. Gray colored ball and stick represent natural ligands with Tamoxifin (Green). (C) The cluster of natural compounds within cavity.

Table-1 Docking result of Tamoxifin and four ligands showing good result out of 18 natural ligands with estrogen receptor (1A52).

No.	Ligand Name	MolDock Score Kcal/mol	Rerank Score	HBond
		Reported Molecule		
1	Tamoxifin	-117.917	-86.9124	-2.5
		Natural Compounds		
2	Epigallocatechin gallate	-135.747	-80.917	0.3520
3	Ginkgetin	-134.482	-46.3557	-3.3677
4	Hyperoside	-137.124	-111.244	-4.8442
5	Ginsenoside	-140.071	-69.1009	-0.8654

Table-2 the drug Likeliness properties of selected natural compounds along with Tamoxifin

	Tamoxifin	Epigallo-catechin gallate	Ginkgetin	Hyperoside	Ginsenoside
Mol.Weight (200-600)	371.51	458.37	566.51	464.38	444.73
H-Donors (0.0-6.0)	0	8	4	8	2
H-Acceptor (0.0-12.0)	2	11	10	12	2
Flexible Bonds (0.0-15.0)	8	4	5	4	4
Rigid bonds (0-50)	19	24	36	24	21
Ring number (0.0-7.0)	3	3	4	3	1
Ring Size (0.0-12.0)	6	10	10	10	17
Carbons (>5.0)	26	22	32	21	30
Heavy Atom (>2.0)	28	33	42	33	32
Ratio of Hetero atom/carbons (0.1-1.0)	0.08	0.50	0.31	0.57	0.07
No of charges (0.0-3.0)	1	0	0	0	0
Total charges (-2.0-2.0)	1	0	0	0	0
Log P (-2.0-6.0)	7.14	2.23	5.69	0.36	8.54
Status	Accepted	Accepted	Accepted	Accepted	،ccepted

CONCLUSION

The structure based docking approach play significant role to propose novel drug or ligand to treat estrogen positive breast cancer. The study indicate that Ginsenoside showing better interaction efficiency against existing drug and having optimal drug like properties. We conclude that this compound may be used as therapeutic agent for treatment of estrogen positive breast cancer.

REFERENCES

Serra K. P., Sarian L. O., Rodrigues-Peres R. M., Vassallo J., Soares F. A., Pinto G. A., Cunha I. W., Shinzato J. Y. and Derchain S. F.; Expression of cyclooxygenase-2 (COX-2) and p53 in neighboring invasive and in situ components of breast tumors ; Acta Histochemica ; 2012; 114: 226– 231

Mishra A.K., Agrawal U., Negi S., Bansal A., Mohil R., Chintamani C., Bhatnagar A., Bhatnagar D. and Saxena S.; Expression of androgen receptor in breast cancer & its correlation with other steroid receptors & growth factors; Indian journal Medicinal Research; 2012; 27: 843-852.

Goodsell D. S.; The Molecular Perspective: Tamoxifen and the Estrogen Receptor; The Oncologist ; 2007; 7:163-164.

Ellis M. J., Coop A., Singh B., Louis M., Llombert-Cussac A., Ja¨nicke F., Miller W. R., Evans D. B., Dugan M., Brady C., Quebe-Fehling E. and Borgs M.; Letrozole Is More

Effective Neoadjuvant Endocrine Therapy Than Tamoxifen for ErbB-1– and/or ErbB-2– Positive, Estrogen Receptor–Positive Primary Breast Cancer: Evidence From a Phase III Randomized Trial; Journal of Clinical Oncology; 2001; 19(18):3808-3816.

Jingmei L., Petra S., Jenny-Chang C., Flesch-Janys D., Liu J., Czene K., Humphreys K. and Per H.; Coffee consumption modifies risk of estrogen receptor negative breast cancer; Breast Cancer Research; 2011; 13.

Jeong E., chung K., Wonshik H., Sung-won K., Seok W. K., Hyuk J. S., Bae J. Y. and Noh

D.Y.; Effect of Estrogen, Tamoxifen and Epidermal Growth Factor on the Transcriptional Regulation of Vascular Endothelial Growth Factor in Breast Cancer Cells; Anticancer Research; 2004; 24: 3961-3964.

http://www.ncbi.nlm.nih.gov/pccompound

http://www.ncbi.nlm.nih.gov/

http://www.ncbi.nlm.nih.gov/pubmed/

http://www.rcsb.org/pdb/home/home.do

http://www.chemspider.com/

http://www.ebi.ac.uk/pdbsum/

http://mobyle.rpbs.univ-paris-diderot.fr:8080/cgi-bin/portal.py?form=FAFDrugs#forms::FAF-Drugs2

http://www.molegro.com/mvd-product.php

Pruitt K. D., Tatusova T. and Maglott D. R.;NCBI reference sequences (RefSeq): a curated non-

redundant sequence database of genomes, transcripts and proteins Nucleic Acids Research; 2007; 35:61–65.

Berman H. M., Westbrook J., Feng Z., Gilliland G., Bhat T. N. , Weissig H., Shindyalov I. N. and Boune P. E.; The Protein Data Bank; Nucleic Acid research; 2000; 28: 235-242.

Laskowski R. A., Chistyakov V. V. and Thornton J. M.; PDBsum more: new summaries and analyses of the known 3D structures of proteins and nucleic acids; Nucleic Acids Research; 2005; 33: 266–268.

Wang Y., Xiao J., Suzek T. O., Zhang J., Wang J. and Bryant S. H.; PubChem: a public information system for analyzing bioactivities of small molecules; Nucleic Acids Research; 2007; 35: 61–65.

❑