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6-GINGEROL FOR CANCER THERAPY- AN *IN SILICO* APPROACH

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ABSTRACT

The natural polyphenolic alkanone 6-gingerol, a major pharmacologically active component of ginger has anti-inflammatory and antitumoral properties. Its potent anti-tumor activity has been reported in a variety of cancer types, including breast, pancreatic, gastric, colon and colorectal cancer and certain hematological malignancies. In a cellular milieu, binding of 6-gingerol with a protein could suppress the cancer cell growth and affect the dynamics of protein-protein interaction thereby altering the structure and function of the protein. In the present study, we identified the potential binding proteins of 6- gingerol for various types of cancer. 6-gingerol was docked to targets – epidermal growth factor receptor (EGFR), oestrogen receptor (ER), Cyclooxygenases (COX-2), Cyclin-dependent kinases (CDKs), and p90 ribosomal protein kinase 2 (RSK2) with the Docking software Discovery studio and docking based virtual screening was attempted.

KEYWORDS: 6-gingerol, EGFR, Oestrogen receptor (ER), Cyclooxygenases (COX-2), Cyclin-dependent kinases (CDKs), p90 ribosomal protein kinase 2 (RSK2) and Discovery studio.

INTRODUCTION

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. All cancers involve the malfunction of genes that control cell growth and division. According to WHOs reports the most commonly diagnosed cancers worldwide were those of the lung (13.0%), breast (11.9%), and colorectum (9.7%).

[6]-gingerol, the major pharmacologically active component derived from ginger, was reported to have antibacterial, antioxidant, antiinflammatory and antitumour properties (Yon Jung Park 2006, Chul- Ho-Jeong, 2009). Several studies suggest that [6]-gingerol is effective in the suppression of the cancer. [6]-gingerol has been found to inhibit the expression of COX-2, lipooxygenases, NF-κB and epidermal growth factor-induced AP-1 activation which play pivotal roles in progression of inflammation and cancer (Sue Ok Kim, 2005, Samuel Joshua Pragasam, 2011). However, the mechanisms by which it prevents cancer are not well understood. The present study attempts to address potential binding proteins of 6- gingerol for various types of cancer.

Various targets used in this study include epidermal growth factor receptor (EGFR), oestrogen receptor (ER), Cyclooxygenases (COX-2), Cyclin-dependent kinases (CDKs), and p90 ribosomal protein kinase 2 (RSK2). The epidermal growth factor receptor belonging to the family of receptor tyrosine kinases, includes EGFR/ErbB1/HER1, ErbB2/HER2/NeuErbB3/HER3, and ErbB4/HER4. These receptors were considered as attractive targets for antitumor studies. EGFR overexpression is thought to play important role in the activation of various malignant tumors (Mayumi Ono, 2006, John Mendelsohn, 2006, John Foley, 2010). Breast cancer is the second most common cancer in women world-wide. The involvement of estrogen in breast cancer has long been recognized (Stephanie Somme, 2001). Cyclooxygenase-2 (COX-2), an inducible prostaglandin is considered as a promising target for the treatment of various human cancers (L R Howe, 2001). COX-2 is aberrantly expressed in colorectal neoplasms. Cyclin dependent kinases (CDKs) are family of protein kinases that are involved in the regulation of cell cycle. CDks are considered as potential target against a wide variety of proliferative diseases, especially cancer (Peter L. Toogood, 2001). p90 ribosomal S6 kinase (RSK2) is a member of a of mitogen-activatedprotein kinase-activatedprotein kinases (MAPKAPKs) family that play an important role in signal transduction.

In this study *in silco* analysis of targets- epidermal growth factor receptor (EGFR), oestrogen receptor (ER), Cyclooxygenases (COX-2), Cyclin-dependent kinases (CDKs), and p90 ribosomal protein kinase 2.

MATERIALS AND METHODS

Ligand preparation

Discovery studio 3.5 was used for the molecular docking studies. 6-gingerol (Mol. Formula $C_{17}H_{26}O_{4)}$ was selected as a ligand, which is more active compound of ginger and it has anti-inflammatory and antitumoral properties. The 3-dimensional structure of 6-gingerol was downloaded in .sdf format PubChem database. It was prepared and filtered by Lipinski and veber rules wizard of software Discovery studio.

Protein Preparation

The X-ray crystallographic 3-dimensional structure of targets- epidermal growth factor receptor (EGFR), oestrogen receptor (ER), Cyclooxygenases (COX-2), Cyclin-dependent kinases (CDKs), and p90 ribosomal protein kinase 2 (RSK2) were downloaded from Protein Data Bank . Protein was prepared based on the CHARMm forcefiled.

Molecular Docking: *In silico* analysis was done with all the prepared proteins using receptor ligand protocol (CDOCKER), and each binding site were docked to understand the molecular interaction of 6-gingerol with EGFR, Oestrogen receptor and RSK2. Docking was simulated with software discovery studio 3.5 client. The interaction between 6-gingerol with EGFR, Oestrogen receptor and RSK2 were analyzed.

RESULTS AND DISCUSSION

Binding site prediction: The active sites were predicted from the target ID's 1XKK (EGFR), 1ERE (ER), 1DDX (COX2), 1CX2 (COX2), 3R9H (CDKs) and 3G51(RSK2) using Discovery studio. Active sites were selected for targets 1XKK, 1ERE, 1DDX, 1CX2, 3R9H and 3G51 to study the ligand interaction.

Docking study: Docking of 1XKK, 1ERE, 1DDX, 1CX2, 3R9H and 3G51 were performed with 6-gingerol and results were analyzed based on C-Docker energy, C-Docker interaction energy, Binding energy, H-Bond, Ligand energy, protein energy and complex energy (Table 1, 2, 3 and 4). Interaction was not obtained for the targets 1DDX and 3R9H.

Table 1- Docking result of 6-gingerol with EGFR (PBD ID: 1XKK)

Site	(-)C-Docker energy	(-)C-Docker interaction energy	H-Bond (Amino acid residues)	Binding energy (kcal/mol)	Protein energy (kcal/mol)	Complex energy (kcal/mol)	Ligand energy (kcal/mol)
1	43.301	53.7262	LYS745 PHE856 PHE856	-82.56933	-10721	-10790.8136	12.84557
4	1.54788	25.1052	ARG748	-35.83247	-10721	-10729.60913	27.31318
8	31.3318	37.1901	ASP1012	-22.24275	-10721	-10738.85025	4.48234

Table 2- Docking result of 6-gingerol with Oestrogen receptor (PBD ID: 1ERE)

Site	(-)C-Docker energy	(-)C-Docker interaction energy	H-Bond (Amino acid residues)	Binding energy (kcal/mol)	Protein energy (kcal/mol)	Complex energy (kcal/mol	Ligand energy (kcal/mol)
1	0.730746	18.5942	ARG394 ARG394 GLU353	-39.41766	-8873.8	-8902.06817	11.11316
2	33.9654	41.2054	SER305 LEU306 GLY366 ASP369	-67.52302	-8873.8	-8935.11648	6.17021
6	6.74732	16.3822	GLU542	-48.55758	-8873.8	-8918.4438	3.87745

Table 3- Docking result of 6-gingerol with RSK2 (PBD ID: 3G51)

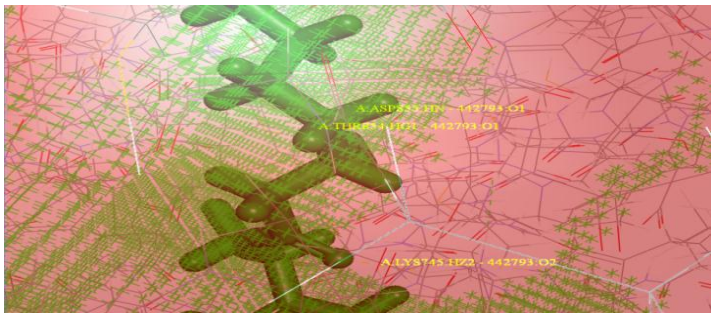
Site	(-)C-Docker energy	(-)C-Docker interaction energy	H-Bond (Amino acid residues)	Binding energy (kcal/mol)	Protein energy (kcal/mol)	Complex energy (kcal/mol	Ligand energy (kcal/mol)
1	41.6589	47.1722	LYS100	-90.9096	-12230	-12317.59441	2.82496
2	28.1268	32.8844	GLY230 THR231	-63.41386	-12230	-12290.41166	2.51197
4	20.426	23.2076	ARG192	-11.41707	-12230	-	0.96015

						12239.96669	
5	38.053	41.0033	LEU285 LYS304	-63.63345	-12230	-12290.27493	2.86829
9	2.00845	11.2439	LYS57	-26.37412	-12230	-12251.05153	4.83236
10	21.6903	22.7001	ILE47	-49.64558	-12230	-12282.02479	-2.86944

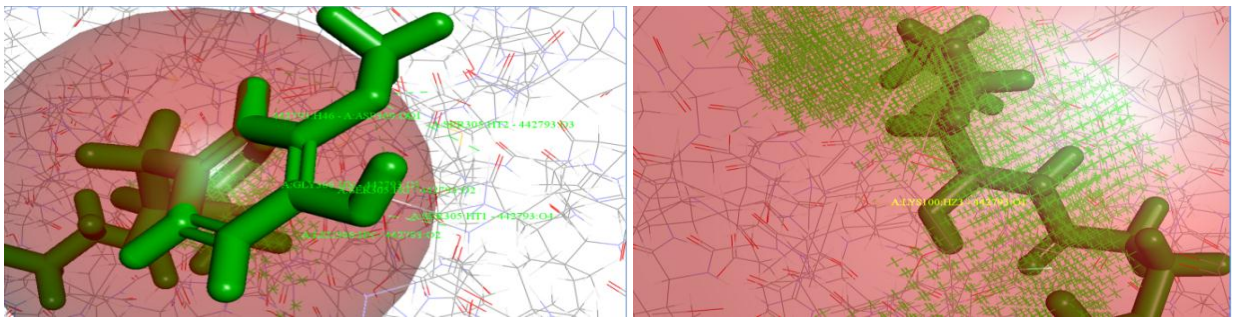
Table 4- Docking result of 6-gingerol with COX-2 (PBD ID: 1CX2)

Site	(-)C-Docker energy	(-)C-Docker interaction energy	H-Bond (Amino acid residues)	Binding energy (kcal/mol)	Protein energy (kcal/mol)	Complex energy (kcal/mol	Ligand energy (kcal/mol)
1	14.6716	17.1241	LYS492	-18.64219	-20046	-20061.98619	2.62866

Binding energy and H-Bonds in the active site indicate the effective stable conformation of the 6-gingerol. The 6-gingerol shown better interaction with active site 1, 4 and 8 of 1XKK, 1, 2 and 6 of 1ERE and 1, 2, 4, 5, 9 and 10 of 3G51.Figures given below showing H-Bond for site 1 in 1XKK, site 2 in 1ERE and site1 in 3G51.



(a)



(b) **(c)**

Fig. 1. (a) Active site 1 of 1XKK with 3 H- Bond; (b) Active site 2 of 1ERE with 6 H-Bond and (c) Active site 1 of 3G51 with 1 H-Bond

Table 5 – ADMET Poperties of 6-gingerol

ADMET Solubility level	ADMET BBB Level	ADMET EXT Hepatotoxic prediction	ADMET Absorption level	ADMET Alog P98
3	2	FALSE	0	3.638

CONCLUSION

In this study 6-gingerol showed better interaction with EGFR, ER and RSK2 with respect to maximum binding energies -82.56933, -67.52302 and -90.9096. The maximum number of H- Bond was found in 1ERE, 1XKK and 3G51. ADMET properties were studied for 6-gingerol with the parameters ADMET Solubility level, ADMET BBB Level, ADMET EXT Hepatotoxic prediction, ADMET Absorption level and ADMET Alog P98 respectively for its toxicity and it conform that we can effectively used 6-gingerol for queering different type of cancers- colon cancer, breast cancer, gastric cancer, pancreatic cancer and skin cancer.

REFERENCES

1. Foleya J, Nickersona N K, Nama S, Allena K T, Gilmorea J L, Nephewa K P and Riese D J. EGFR signaling in breast cancer: Bad to the bone. J 2010; 21: 951-960.
2. Howe L R, Subbaramaiah K, Brown A M Cand Dannenberg A J. Cyclooxygenase-2: a target for the prevention and treatment of breast cancer. Endocrine-Related Can. 2001; 8: 97–114.
3. Jeong C H, Bode A M, Pugliese A, Cho Y Y, Kim H G, Shim J H, Jeon Y J, Li H, Jiang H and Dong Z. [6]-Gingerol Suppresses Colon Cancer Growth by Targeting Leukotriene A_4Hydrolase. Canc. Res. 2009; 69: 5584-5591.
4. Kim S O, Kundu J K, ShinY K, Park J H, Cho M H, Kim Y T and Surh Y J. [6]-Gingerol inhibits COX-2 expression by blocking the activation of p38 MAP kinase and NF-jB in phorbol ester-stimulated mouse skin. Oncogene 2005; 24: 2558–2567.
5. Macari E A, Goven D, Brayer S, Hamimi A, Besnard V, Somme J M, Ali Z E, Crestani B, Römer S K, Boutten A and Bonay M. Nuclear Factor Erythroid 2-Related Factor 2 Nuclear Translocation Induces Myofibroblastic Dedifferentiation in Idiopathic Pulmonary Fibrosis. ANTIOXIDANTS & REDOX SIGNALING 2013; 18.
6. Meldensohn J and Baselga J. Epidermal Growth Factor Receptor Targeting in Cancer. Seminoncol. 2006; 04. 003.
7. Ono M and Kuwano M. Molecular Mechanisms of Epidermal Growth Factor Receptor (EGFR) Activation and Response to Gefitinib and Other EGFR-Targeting Drugs. Clin Cancer Res 2006; 12: 7242-7251.
8. Park Y J, Wen J, Bang S, Park S W and Song S Y. [6]-Gingerol Induces Cell Cycle Arrest and Cell Death of Mutant p53-expressing Pancreatic Cancer Cells. Yonsei Med J. 2006; 47(5): 688-697.
9. Pragasam, Joshua S, Kumar, Suresh, Bhoumik, Mayurika, Sabina, Evan Prince, Rasool and Mahaboobkhan. 6-Gingerol, an active ingredient of ginger suppresses monosodium ureate crystal-induced inflammation: An in vivo and in vitro evaluation. Annals of Bio. Res. 2011; 2(3): 200-208.
10. Toogood P L. Cyclin-dependent kinase inhibitors for treating cancer. J 2001; 21(6): 487-498.