



Molecular Docking Study of Quercetin Analogues for Treating Tumours

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Abstract : Drug discovery leading to robust and viable lead candidate's remains a challenging scientific task, which is the transition from a screening hit to a drug candidate, requires expertise and experience. Natural products and their derivatives have been recognized for many years as a source of therapeutic agents and of structural diversity. The present research attempts to describe the utilization of compounds derived from natural resources as drug candidates, with a focus on the success of these resources in the process of finding and discovering new and effective drug compounds, an approach commonly referred to as "natural product drug discovery".¹

Introduction:

Estrogen receptor alpha (ER α), also known as NR3A1 (nuclear receptor subfamily 3, group A, member 1), is one of two main types of estrogenreceptor, a nuclear receptor that is activated by the sex hormone estrogen. In humans, ER α is encoded by the gene ESR1 (Estrogen Receptor 1).¹

The estrogen receptor (ER) exists in two forms known as ER alpha and ER beta. Currently, a clinical role has only been established for ER alpha. The primary use of ER alpha in breast cancer is for predicting likely response to hormone treatment. Patients with breast cancers expressing ER alpha are approximately seven to eight times more likely to benefit from endocrine therapy than ER alpha-negative patients. For the initial three to five years after primary diagnosis, ER alpha-positive patients generally have a better outcome than ER alpha-negative patients. Overall, however, the prognostic value of ER alpha is relatively weak and only of limited value in the clinically important subgroup of patients with lymph node-negative disease. Further work is required to establish if ER beta has a clinical role in breast cancer^[12]

Estrogen receptors (ERs) are a group of proteins found inside cells. They are receptors that are activated by the hormone estrogen (17 β -estradiol).

S.Gejalakshmi *et al* //International Journal of PharmTech Research, 2019,12(4): 30-34.

DOI: <http://dx.doi.org/10.20902/IJPTR.2019.120405>

Estrogen receptors are over-expressed in around 70% of breast cancer cases, referred to as "ER-positive", and can be demonstrated in such tissues using immunohistochemistry. Two hypotheses have been proposed to explain why this causes tumorigenesis,² and the available evidence suggests that both mechanisms contribute:

- First, binding of estrogen to the ER stimulates proliferation of mammary cells, with the resulting increase in cell division and DNA replication, leading to mutations.
- Second, estrogen metabolism produces genotoxic waste

Human Epidermal Growth Factor Receptor

Description:

The protein encoded by this gene is a transmembrane glycoprotein that is a member of the protein kinase superfamily. This protein is a receptor for members of the epidermal growth factor family. EGFR is a cell surface protein that binds to epidermal growth factor. Binding of the protein to a ligand induces receptor dimerization and tyrosine autophosphorylation and leads to cell proliferation.^[3-7]

Approximately half cases of triple-negative breast cancer (TNBC) and inflammatory breast cancer (IBC) overexpress EGFR. Thus, EGFR inhibitors for treatment of breast cancer have been evaluated in several studies.^[8]

Drug Likeness Testing⁹⁻¹³:

DruLiTo was used to test the drug likeness property of the molecule, the results are tabulated as follows;

Selected Filters	Total Number of Molecule Filter	Total Number of Molecule Violated the Rule
Lipinskies Rule of Five	1	0
Ghose Filter	1	0
CMC – 50 Like Rule	1	0
Vebers Rule	0	1
MDDR Like Rule	0	1
BBB Likeness Rule	0	1
Unweighted QED	1	0

Receptor preparation:

The well-defined 3d structure of Estrogen receptor alpha ligand-binding domain complexed to estradiol was download from RCSB PDB (<http://www.rcsb.org>), It consist of code 1A52. Receptor structure is downloaded in pdb format so as to view in Argus lab.

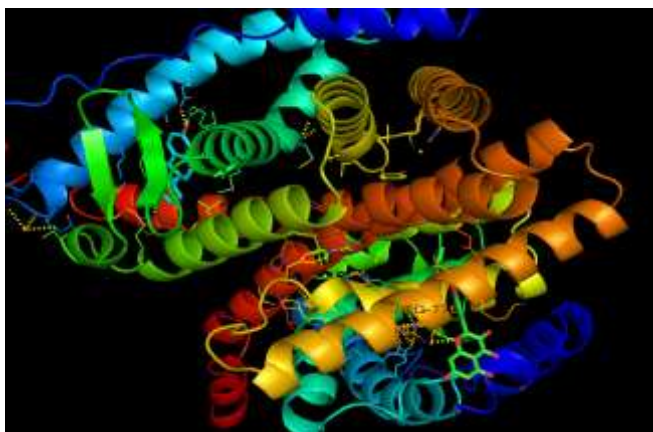
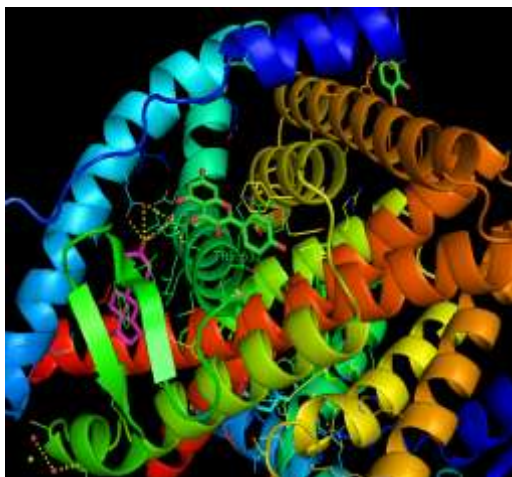
Ligand preparation:

Bioactive quercetin compound is obtained from *Hypericum formosanum* was selected as ligand for receptor Estrogen receptor alpha ligand-binding domain complexed to estradiol. The ligand structure is drawn using chemsketch software, its 3d structure viewed in Argus lab.

Molecular docking:

Initially some active sites of receptor Estrogen receptor alpha ligand-binding domain complexed to estradiol were identified such as 380GLU, 520LYS, 526TYR, 632TRP, 716ARG based on earlier studies. The docking study was made on ArgusLab 4.0.1 from Mark Thompson and Planariasoftware LLC. The docking is studied in grid dimension(x, y, z) of 39×39×39. The docking study is analysed in basis of best ligand pose and are active sites are ranked on basis of it. Further dockings were visualized in Pymol viewer.

S.No	Rank	Active Site	Best Ligand Pose Energy (KCal/Mol)	Cluster Poses
1	1	632TRP	-7.21194	86
2	2	380GLU	-6.6713	94
3	3	520LYS	-6.3629	62
4	4	526TYR	-6.22825	109
5	5	716ARG	-6.17315	95



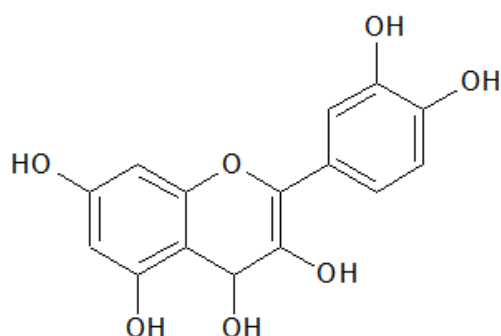
Result and Discussion:

Molecular study is mainly to predict the specific ligand interaction and binding energy with amino acid of receptor. Docking study is made with help of Argulab software, automated docking made with selected amino acids which gives the binding poses energy (Kcal/mol). Lowest bind energy is considered as best binding area. Quercetin ligand binds with an amino acids such as 632 TRP,380GLU,520LYS,526TYR,716 ARG with binding poses energy of -7.211, -6.671, -6.362,- 6.228, -6.173 respectively. From the docking study, quercetin is bindedwith receptor 1A52, Therefore it may use for synthesis of anticancer.

Conclusion:

The result of docking study shows that the quercetin obtained from extraction of *Hypericumformosanum* can be use for reduction of cancer.The aromatic aldehyde derivative formed between Gly238 and hydroxyl of aldehyde of chromones,the bond length was found to be -1.1 near aromatic substitution of chromone substitution. The aromatic aldehyde derivative formed between Phe239 and hydroxyl of aldehyde of chromones,the bond length was found to be 1.4A⁰ near aromatic substitution of chromone substitution. The other hydrogen was found between Ly2 andhydroxy group of chromonederivatives.The bond length was found to be—4.8 A⁰ aromatic substitution of chromonederivatives.The active site is present in A ring of the protein. The residue bind with the ligand is same as that of the standard compounds docked. The residues found in the active sites are as follows 632 TRP,380GLU,520LYS,526TYR,716 ARG.

Ligand: Quercetin



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