ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 17, Issue 1, 2024

Online - 2455-3891
Print - 0974-2441

Short Communication

MOLECULAR DOCKING STUDY OF EPIGALLOCATECHIN GALLATE ON FLT3 IN COMPLEX WITH GILTERITINIB FOR ANTICANCER ACTIVITY

THOMAS KURIAN*

Department of Medical Education, College of Pharmacy Government Medical College, Kottayam, Kerala, India.
***Corresponding author: Thomas Kurian; Email: thomaskurian54@gmail.com**

Received: 20 June 2023, Revised and Accepted: 07 August 2023

ABSTRACT

Objective: The aim of the study was to predict the binding affinity and interaction patterns between EGCG and FLT3 in complex with gilteritinib using molecular docking simulations. stabilization of the EGCG-FLT3-gilteritinib complex.

Methods: The crystal structure of FLT3 in complex with gilteritinib was downloaded from the Protein Data Bank (PDB) database. Epigallocatechin gallate (EGCG) was obtained from the PubChem database. Auto Dock 8 software was utilized for the molecular docking study. The docking results are analyzed to identify the best pose based on binding affinity, hydrogen bonding, and other favorable interactions. The Discovery Studio Visualizer or other suitable software was used to visualize the protein-ligand interactions and analyze the binding mode of EGCG within the FLT3-gilteritinib complex.

Results: The best ranking for ligands binding was at run 7 with the estimated free energy of binding −7.87 kcal/mol the estimated inhibition constant (ki) was 1.69 µm. The final intermolecular energy was −11.45 kcal/mol. kcal/mol It had 12 active torsions. The redocking score using gilteritinib was used as a control for the validation of the study. The estimated free energy of binding was −7.91 kcal/mol. The estimated inhibition constant ki is 1.60 µm. It had nine active torsions.

Conclusion: Comparing the various binding energies and torsions of the test compound and the control revealed that the test epigallocatechin had a perfect docking score, and it was predicted to possess comparable anti-tumor and anticancer activity.

Keywords: Cancer, Epigallocatechin gallate, Auto dock, Molecular docking.

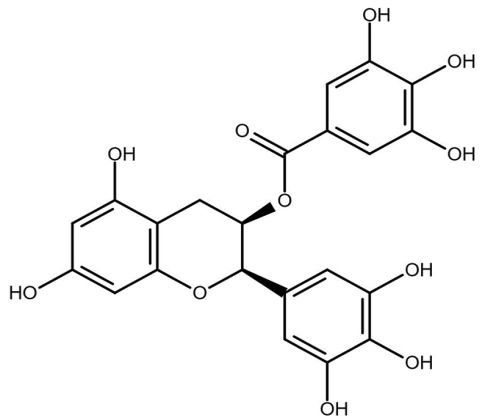
 DOI: http://dx.doi.org/10.22159/ajpcr.2024v17i1.48733. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Green tea camellia sinensis contains caffeine, polyphenols, and tannins. The health benefits of green tea are anti-inflammatory, antiarthritic, anticancer, antibacterial, antioxidant, antiviral, and neuroprotective properties [1].

The presence of abundant catechin makes it an excellent health Supplement.

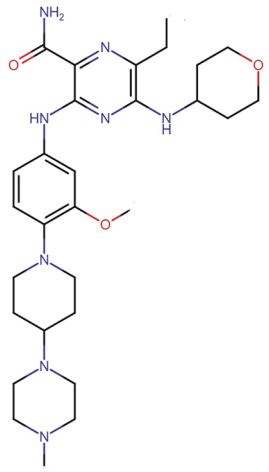
Green tea is made from the unfermented leaf of camellia sinensis. Some experimental evidence suggests that green tea extract has the property of decreasing the risk of prostate cancer. Other studies indicated a lower occurrence of new cancer cases in people consuming green tea [2]. Epigallocatechin, the active constituent of green tea possess anticancer activity, especially in multiple myeloma [3] and induces apoptosis of various cancer cells [4].



Epigallocatechin - 3 -Gallate (EGCG)

IUPAC ID: [(2R, 3R)- 5,7-dihydroxy-2-(3,4,5- trihydroxy phenyl) chroman -3 yl] 3,4,5- trihydroxy benzoate [5].

Molecular formula $C_{22}H_{18}O_{11}$ Pub chem CID 65064



Gilteritinib PubChem CID 49803313

Molecular docking is a vital tool in structural biology and computational chemistry. It predicts the predominant binding modes of the ligand with a protein. It is used to perform virtual screening of a large number of compounds and rank the results and predict the biological activities and mechanism of action of various phytocompounds and synthetic chemical compounds [6]. In-depth study of genetics and molecular biology has yielded increasing molecular targets for anticancer drug

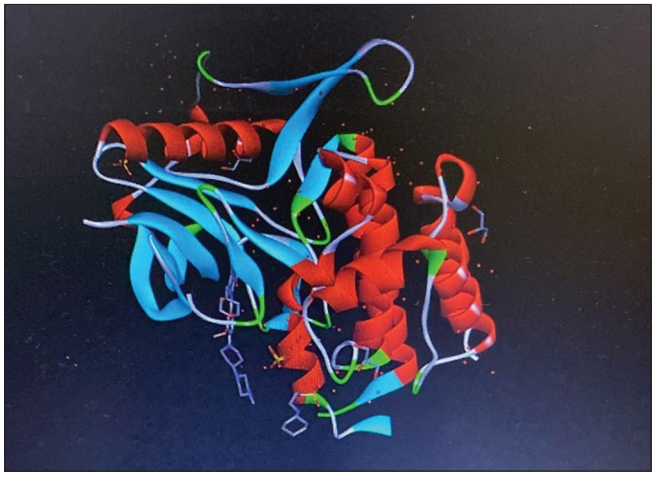


Fig. 1: Crystal structure of FLT3 in complex with Gilteritinib - classification transferase organism Homo sapiens

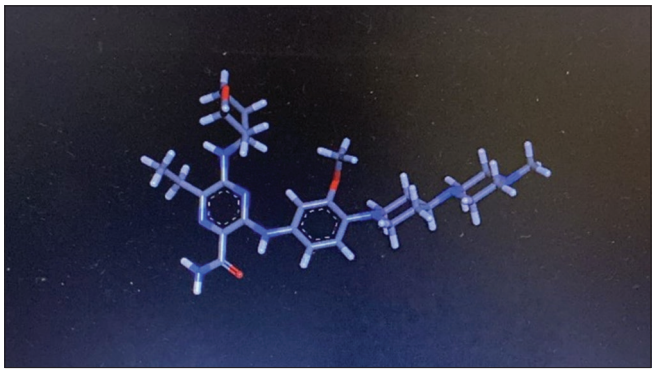


Fig. 2: Gilteritinib (redocking control)

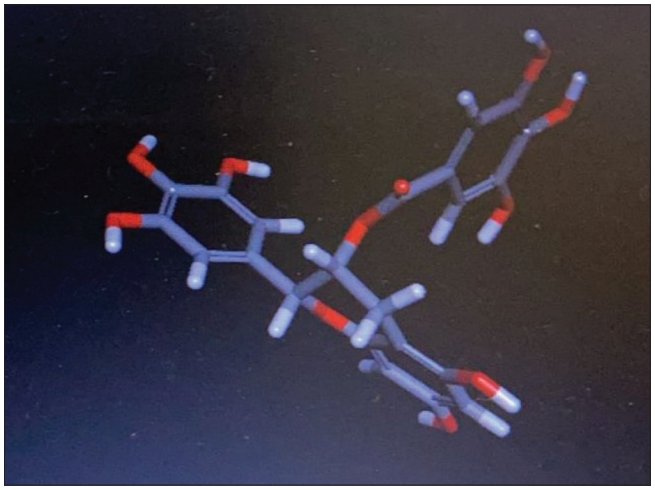


Fig. 3: Ligand epigallocatechin gallate

discovery and development. Structure-based drug design is one of the most prominent methods for identifying compounds exhibiting more specific anticancer activities.

The database provides chemical structures of phytochemicals and synthetic molecules, which are considered for various molecular docking studies. Software like auto dock and Pyrex offer a free platform for performing molecular Docking using phytochemicals to obtain their possible pharmacological actions [7].

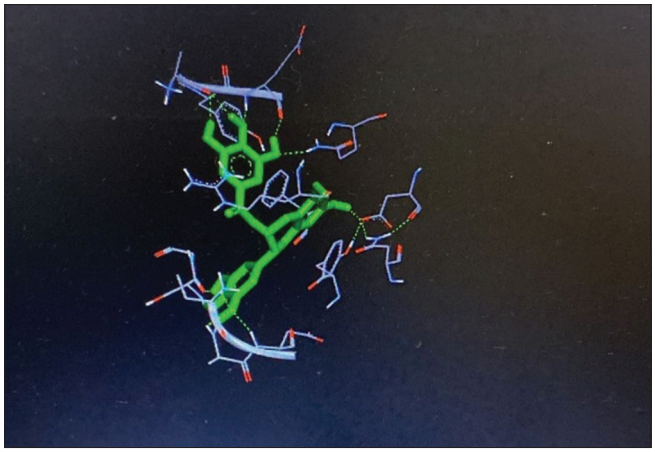


Fig. 4: Docked images

Table 1: Binding energies (docking score) of gilteritinib in different runs and ranking

Binding energy	Rank	Run Number
−7.91	1	2
−7.67	2	7
−7.38	3	3
−6.80	4	6
−6.66	5	5
−6.28	6	4
−6.28	7	1

Table 2: Binding energies (docking score) of epigallocatechin gallate in a different run and –ranking

Binding energy	Rank	Run number
−7.87	1	7
−6.93	2	4
−6.00	3	1
−5.36	4	8
−5.36	5	9
−5.25	6	2
−4.86	7	1

METHODS

Ligand preparation

The ligand epigallocatechin three gallate (PubChem CID 65064) was downloaded from the PubChem database in Sdf format (Fig. 3). The structure was drawn using a chem sketch saved in mol format. The system is opened in the Drug Discovery studio, and added polar Hydrogen is saved as Protein Data Bank (PDB) files and finally as PDBQT form.

Receptor preparation

Protein was downloaded from PDB website Protein ID (6jQR) in PDB format in 3D form (Fig. 1). Deleted water molecules and added polar Hydrogen, and saved in PDB format. Added charges and saved as PDBQT format.

Control preparation for validation by redocking

The control, which was removed from the target, was prepared like the ligand and saved in PDBQT format. The reference used was Gilteritinib Gliteritinib (Fig. 2).

Running grid and docking

The grid could be run using executable files auto grid 4.exe and auto dock 4. exe. using commands. Docking preparation could be done by generating pdf and log files [8].

RESULTS

The conformations were played and analyzed using the Discovery studio visualizer Gliteritinib (Fig. 4). The binding energies were analyzed. Binding energy combines inter-molecular energy, final total energy, and torsional free energy unbound system energy.

The docking scores (Binding energy) were compared and ranked using a histogram (Table 1). The ranking was based on the least energy (most negative score), which gave the best result (Table 2). The result was interpreted based on the score and the functions of the target in biological activity.

DISCUSSION

Molecular docking studies the interaction between a ligand (drug) and a target (Protein/Enzyme/gene). It predicts how a target would interact with a small molecule (ligand). It will give information about ligands' orientation in the protein binding site. Here, the interaction between epigallocatechin-3-gallate, which is a crucial constituent of green tea, is selected as a ligand, and its interaction with target FLT3 (PDBID 6jQR), which is in combination with gilteritinib. The receptor preparation removed the gilteritinib from the target, and it was further prepared and used for redocking and validation. The target is a tyrosine protein kinase inhibitor. The best ranking for ligands binding was at run 7 with the estimated free energy of binding −7.87 kcal/mol). The estimated inhibition constant (ki) was 1.69 μm. The final intermolecular energy was −11.45kcal/mol. The final total internal energy was −4.96 kcal/mol. The torsional force energy was +3.58 kcal/mol. Unbound systems energy was −4.96 kcal/mol. It has 12 active torsions. The redocking score using gilteritinib was used as a control for the validation of the study. The estimated free energy of binding was −7.91 kcal/mol. The estimated inhibition constant ki is 1.60 μm. The final intermolecular energy was −10.59 kcal/mol Final total internal energy was −2.92. The torsional free energy was +2.68 kcal/mol unbound system energy was −2.92 kcal/mol. It had nine active torsions.

CONCLUSION

Comparing the various binding energies and torsions of the test compound and the control revealed that the test epigallocatechin had a perfect docking score, and it is predicted to possess comparable anti-tumor, and anticancer activity, especially in multiple myeloma and induce apoptosis of various cancer cells.

AUTHORS CONTRIBUTION

Dr. Thomas Kurian gave full effort to complete the manuscript.

CONFLICTS OF INTEREST

The researcher claims no conflicts of interest.

AUTHORS FUNDING

This research did not receive any funding from any agencies in public, commercial, or non-profit organizations.

REFERENCES

1. Chacko S, Thambi PT, Kuttan R, Nishigaki I. Beneficial effects of green tea: A literature review. Chin Med 2010;5:13. doi: 1186/1749-8546-5-13, PMID 20370896
2. Filippini T, Malavolti M, Borrelli F, Izzo AA, Fairweathert-Tait SJ, Horneber M, *et al*. Green tea (*Camellia sinensis*) for the prevention of cancer. Cochrane Database Syst Rev 2020;3:CD005004. doi: 10.1002/14651858.CD005004, PMID 32118296
3. Zhou CG, Hui LM. Epigallocatechin gallate inhibits the proliferation and induces apoptosis of multiple myeloma cells via inactivating EZH2. Eur Rev Med Pharmacol Sci 2008;22:2093-8. doi: 10.26355/eurrev_201804_14742, PMID: 29687868
4. Nakazato T, Ito K, Ikeda Y, Kizaki M. Green tea component, catechin, induces apoptosis of human malignant b cell via production of reactive oxygen species. Clin Cancer Res 2005;11:6040-9. doi: 10.1158/1078-0432.CCR-04-2273, PMID: 16115949
5. Zhang J, Cui H, Qiu J, Wang X, Zhong Y, Yao C, *et al*. Stability of glycosylated complex loaded with Epigallocatechin 3-gallate (EGCG). Food Chem 2022;410:135364. doi: 10.1016/jfoodchem.2022.135364, PMID 36623458
6. Morris GM, Lim-Wilby M. Molecular docking. Methods Mol Biol 2008;443:365-82. doi: 10.1007/978-1-59745-177-2_19, PMID18446297
7. Geromichalos GD. Importance of molecular computer modelling in anticancer drug development J BUON 2007;12 Suppl 1:S101-18. PMID: 17935268
8. Huey R, Morris GM, Forli S. Using AutoDock4 and Auto Dock Vina with Auto Dock Tools: A Tutorial. California, USA: The Scripps Research Institute, Molecular Graphic Laboratory; 2012. p. 5-19.