DOI 10.18699/SBB-2022-207

Nigella sativa compounds as novel EGFR inhibitor using DFT, molecular docking and molecular dynamics

Tufail A.[1]*, Dubey A.[2, 3]*

[1] *Department of Biochemistry, University of Allahabad, Allahabad, India*

[2] *Computational Chemistry and Drug Discovery Division, Quanta Calculus Pvt. Ltd., Kushinagar, India*

[3] *Department of Pharmacology, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, India*

** aishatufailansari@gmail.com, ameetbioinfo@gmail.com*

Key words: EGFR, *Nigella sativa*, DFT, Molecular Docking, Molecular Dynamics

Motivation and Aim: Health problems are increasing around the globe regarding cancer modalities. With approximately 10 million deaths expected in 2020, cancer is the leading cause of death worldwide [1]. The epidermal growth factor receptor (EGFR; HER1 in humans) is a transmembrane protein that belongs to extracellular protein ligands. Mutations that impact EGFR expression or function have the potential to cause cancer in a variety of cancer types. Over expression of EGFR is linked to the development of a range of malignancies, while faulty EGFR signaling is linked to disorders including Alzheimer's. The patient condition can be improved by preventing the growth of EGFR tumors. This can be accomplished by either blocking the EGFR receptor sites or by inhibition of its intracellular tyrosine kinase activity [2]. For cancer treatment, EGFR can be used as a promising target for the discovery of novel drugs [3]. As a result, computer-assisted research was used to find effective inhibitors of the EGFR receptors. Plants have been utilized as a significant part of treatment for a variety of disorders all around the world for ages [4]. Many plants have been proven to have potential therapeutic activity without undesired effects. Hence, it has created a strong desire to identify compounds from plants that have been used to treat ailments for centuries. The application of new approaches to an established old discipline may lead to the discovery of effective medications [5]. A plant of the family Ranunculaceae known as *Nigella sativa* is a widely used medicinal plant throughout the globe [6]. *Nigella sativa* seeds have long been used to cure a variety of ailments. To evaluate the potential ability of compounds from *N. sativa* to bind EGFR receptor, we used a computational approach based on Molecular docking, Density Function Theory (DFT), and Molecular Dynamics (MD) simulations. The findings showed that *N. sativa* compounds can bind to the human EGFR receptor's active site residues. Alpha-herederin, in instance, exhibited a projected binding energy that was equivalent to or better than certain existing medicines and interacted well with critical amino acids in the EGFR active site region. Our findings also indicate that several *N. sativa* compounds may be act as effective EGFR receptor inhibitors. We feel compelled to pursue this result further in the development of a possible medication and therapeutics in cancers.

Methods and Methodology: We came across *N. sativa* compounds. On the investigated compounds, DFT calculations were performed, as well as geometry optimizations, and Molecular Electrostatic Potential (MESP) map. Following DFT calculations, optimized structures underwent through molecular docking calculations. In the Protein Data Bank (https://www.rcsb.org/), we find the crystal structure of EGFR receptor complexes with

its known inhibitor (PDB code 1I8I). Pubchem (https://pubchem.ncbi.nlm.nih.gov/) was used to download the 3D structures of active compounds from *N. sativa* as well as known drugs as controls (temozolomide, lapatinib, and procarbazine) that have activity against brain tumors. Auto Dock version 1.5.7 and Maestro (Schrodinger suit) were used to prepare and dock the receptor and *N. sativa* compounds. Docking simulations using Auto Dock were set up according to the instructions in the studies. The protein structures of Maestro (Schrodinger suit) were created using the protein preparation wizard designed for this program, and explicit hydrogen were added. Using its cavity identification algorithm, this application automatically detects possible binding sites (active sites).The conformations of the best poses for each molecule examined were chosen, recorded in.pdb format, and assessed for interactions with the receptor using the Discovery Studio tools. Simulations of molecular dynamics MD simulations lasting 100ns were carried out on a Linux cluster computer running the MD application.

Results: The bulk of the chemical compounds identified from *N. sativa* are projected to bind the EGFR receptor with binding energies equivalent to, if not better than, recognized brain tumor treatments. All of the compounds selected from *N. sativa* have a negative binding energy, indicating a potential ability to interact with the receptor (Table 1). According to the analysis, the best-predicted-energy complexes show that these compounds can interact with critical residues involved in substrate binding and catalysis.

Table 1. Shows the results of ligand docking simulations in the active site of the EGFR receptor. The representative pose of the cluster of solutions discovered corresponds to the best-predicted binding energy. For procarbazine, temozolomide, and lapatinib, the projected binding energy of the representative posture and the number of poses of the associated cluster are used as a comparative control

Compounds Pubchem ID	Auto dock		Maestro (Schrodinger)	
	No of poses	Binding energy kcal/mol	XP Score	Glide Emodel
Controls for analysis				
Procarbazine(4915)	47	–6.24	–3.676	–39.851
Temozolomide (5394)	18	–5.86	–5.326	–39.384
Lapatinib (208908)	91	–6.76	–2.071	–72.140
Nigella sativa compounds				
Alpha-herederin (73296)	28	–7.27	–6.417	–59.382
Nigellidine (136828302)	99	–7.11	–3.322	–38.204
Thymol (6989)	100	–5.18	–3.832	–24.566
Thymoquinone (10281)	77	–5.17	–4.640	–21.810
Thymohydroquinone (95779)	91	–4.88	–4.640	–28.082

Conclusion: The goal of this study was to find novel EGFR receptor inhibitors from *N. sativa* that will bind to the receptor's active site selectively. Alpha-heredin was discovered to be one of the chemical compound with the potential to bind to the EGFR receptor. The docking method also identified nigellidine as a possible receptor ligand. MD simulations corroborated the docking research that nigellidine may bind stably to the receptor's active site, while the result for Alpha-herederin did not match docking results completely. The ability of nigellidine and α-herederin to persist in the active site of the EGFR receptor suggests that modifying this compound to improve its specificity and affinity could lead to the identification of a new compound of EGFR inhibitors. As a result, we believe that this research will serve as a first step toward the creation of new EGFR inhibitors for the treatment of brain cancers.

References

1. Ferlay J., Ervik M., Lam F., Colombet M., Mery L., Piñeros M. et al. Global cancer observatory: cancer today. Lyon: International Agency for Research on Cancer, 2020. (https://gco.iarc.fr/today). Accessed February 2021.
2. Sinto S., Settleman J., Reshkin S.J., Azzariti A., Bellizzi A., Paradiso A. The complexity of targeting EGFR signalling in cancer: From expression to turnover. *Biochim Biophys Acta Bioenerg.* 2006;1766:120-39. doi: 10.1016/j.bbcan.2006.06.001.
3. He K., Xu J., Liang J., Jiang J., Tang M., Ye X., Zhang Z., Zhang L., Fu B., Li Y., Bai C., Zhang L., Tao W. Discovery of a novel egfr-targeting antibody-drug conjugate, SHR-A1307, for the treatment of solid tumors resistant or refractory to anti-egfr therapies. *Mol Cancer Ther*. 2019;18(6):1104-1114.
4. Ahmad A., Husain A., Mujeeb M., Khan S.A., Najmi A.K., Siddique N.A., Damanhouri Z.A., Anwar F. A review on therapeutic potential of *Nigella sativa*: A miracle herb. *Asian Pac J Trop Biomed*. 2013;3(5):337-52.
5. Dubey A., Dotolo S., Ramteke P.W., Facchiano A., Marabotti A. Searching for chymase inhibitors among chamomile compounds using a computational-based approach. *Biomolecules*. 2018;9(1):5. doi: 10.3390/biom9010005.
6. Ahmad A., Husain A., Mujeeb M., Khan S.A., Najmi A.K., Siddique N.A., Damanhouri Z.A., Anwar F. A review on therapeutic potential of *Nigella sativa*: A miracle herb. *Asian Pac J Trop Med.* 2013;3(5):337-352. doi: 10.1016/S2221-1691(13)60075-1.