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Research Article

In- Silico Analysis to Access the Antibacterial Effect of Genistein: Molecular Docking Approach

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Abstract: Much of the current interest in the pharmacology and physiology of these bioactive phytochemicals has focused on the class of isoflavones. Genistein (5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one) is a phytoestrogen that is found in a wide variety of plant-derived foods. Genistein has varieties of health benefits. It is found to be a potent antioxidant agent used along in both prophylaxis and treatment of cancer and various other chronic diseases. Dihydrofolate reductase inhibitors are an important class of drugs, as evidenced by their use as antibacterial, antimalarial, antifungal, and anticancer agents. Dihydrofolate reductase (DHFR, EC 1.5.1.3) is one of the enzymes active in the folate cycle which plays an important role in DNA synthesis. Inhibition of DHFR is an important element in the treatment of many diseases, including cancer and AIDS related infections. A search for new selective inhibitors is motivated by the resistance to common drugs observed in the course of treatment. In this paper an attempt has been made to find new DHF inhibitor by molecular docking. The Genistein strictly follows Lippinski's rule of five, thus having very good drug score as well as drug likeness score. The result access the anti-bacterial activity of Genistein by molecular docking approach by comparing with standard ligand Salinamide (SAL).

Keywords: Dihydrofolate reductase(DHFR), Genistein,Molecular docking & Antibacterial.

INTRODUCTION

Molecular docking is one of the most often used methods in SBDD because of its ability to predict, with a substantial degree of accuracy, the conformation of small-molecule ligands within the appropriate target binding site. Following the development of the first algorithms in the 1980s, molecular docking became an essential tool in drug discovery. In addition, molecular docking algorithms execute quantitative predictions of binding energetics, providing rankings of docked compounds based on the binding affinity of ligand-receptor complexes. The identification of the most likely binding conformations requires two steps: (i) exploration of a large conformational space representing various potential binding modes; (ii) accurate prediction of the interaction energy associated with each of the predicted binding conformations. Molecular docking programs perform these tasks through a cyclic process, in which the ligand conformation is evaluated by specific scoring functions. This process is carried out recursively until converging to a solution of minimum energy (Strategies, L. *et al.*, 2015). Within folate metabolism, Dihydrofolate reductase (DHFR) which catalyzes the reduction of folate or 7, 8-dihydrofolate to te trahydrofolate and intimately couples with thymidylate synthase has been of particular curiosity. The DHFR is present in all cells and is necessary for the maintenance of intracellular folate pools in a biochemically active reduced state . Inhibition outcome in depletion of intracellular reduced folates, which are necessary for one carbon transfer reactions. One carbon transfer reactions are important for the biosynthesis of thymidylate, purine nucleotides, methionine, serine, glycine and many other compounds necessary for RNA, DNA and protein synthesis. Therefore, DHFR represents an attractive target for developing new antibacterial & antitumor agents (Vivek, Srivastava, *et al.*, 2008). Flavonoid is major phenolic compounds are becoming the major subject of medical

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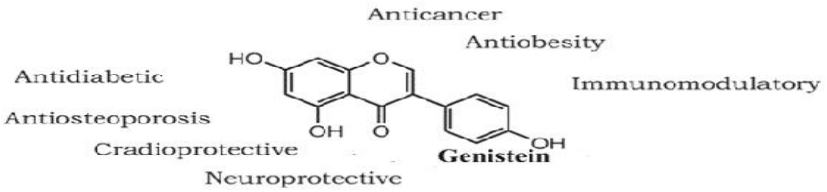
research. They have been reported to possess many useful properties, including oestrogenic activity, anti-inflammatory activity, enzyme inhibition, antimicrobial activity (Himesh, Soni, *et al.*, 2014). Genistein is a soy derived isoflavanoid compound with large number of health benefits. Genistein is a common form of phytoestrogens that are found in a variety of plants, especially in soy. Phytoestrogens are a group of plant substances that have a chemical structure similar to estrogen, exerting estrogenic and antiestrogenic effects (Ajaz, A.G, *et al.*, 2015).Various pharmacological effect of Genistein are as follow:



Genistein [4′, 5, 7-trihydroxyisoflavone or 5, 7-dihydroxy-3-(4-hydroxyphenyl) chromen-4-one] ($C_{15}H_{10}O_5$) belongs to a multifunctional natural isoflavonoid class of flavonoids with a 15-carbon skeleton. The chemical structure of genistein is similar to estradiol[5]. One of the important objectives of QSAR is to get useful information for the synthesis of more active or less toxic compounds. QSAR has correctly predicted the activity of large number of compounds before their synthesis[6].Taking all aspects in literature survey an attempt had been made in study binding affinity of genistein to DHFR for development potent DHFR inhibitor which possess various pharmacological effects.

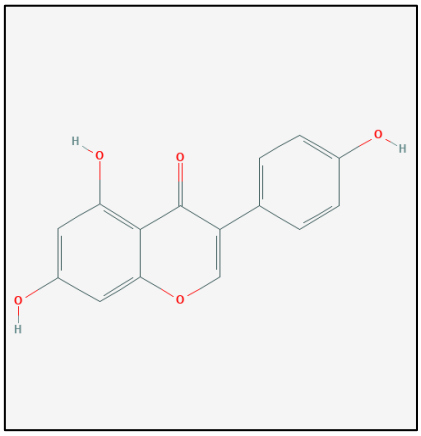
MATERIAL AND METHOD

Molecular Docking Simulations

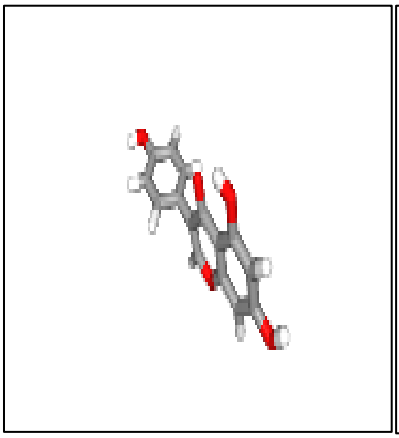
All the calculations were carried out by using Autodock 4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of *Pymol*, *Chimera*, *DS visualizer*, *MMP Plus*.

LIGAND PREPARATION

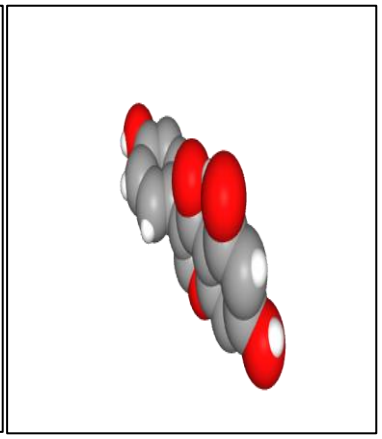
2D Structure of ligand (Geinistein) was drawn using ChemSketch, the two-dimensional structure of was converted into 3-D structure and optimized with 3D geometry. The optimized structure was saved in PDB format for AutoDock compatibility. The basic structure of ligand (Geinistein) is given below:



2D structure of Genistein



Stick model



Space fill model

PREPARATION OF THE GRID FILE

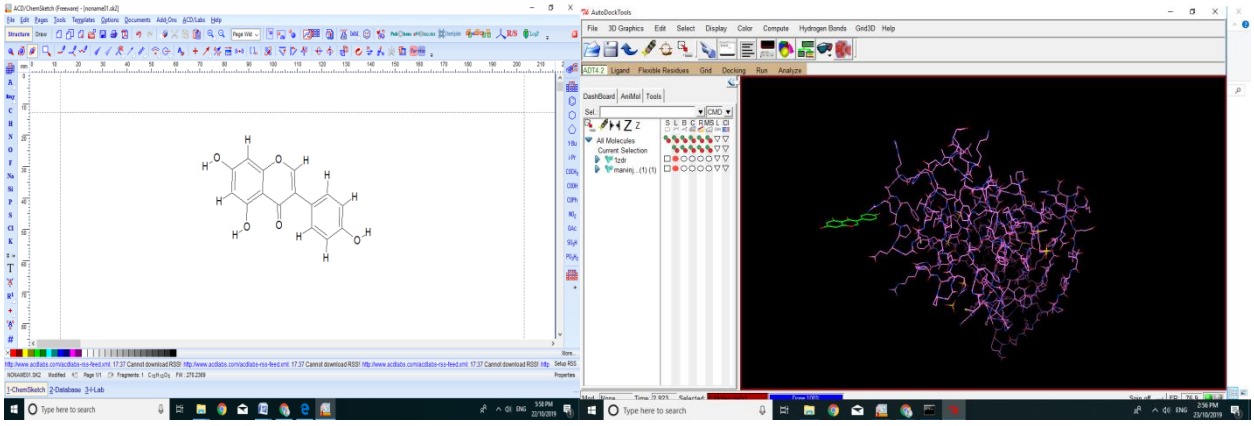
The regions of interest used by AUTODOCK were defined by considering grid area by making a grid box around the active sites. Grid box plays a central role in process of docking as it is made to cover all the amino acids present in active sites necessary for binding other than those present in receptor. Grid box has 3 thumbwheel widgets which let us change the number of points in the x, y and z dimensions. The spacing between grid points can be adjusted with another thumbwheel, the value in the study taken is 0.714 Å and No. of points considered are 60, 60 and 60 points in the x, y, and z dimensions and -29.103, 167.828 and 54.634asx, y, z, centres.

Preparation of the docking file

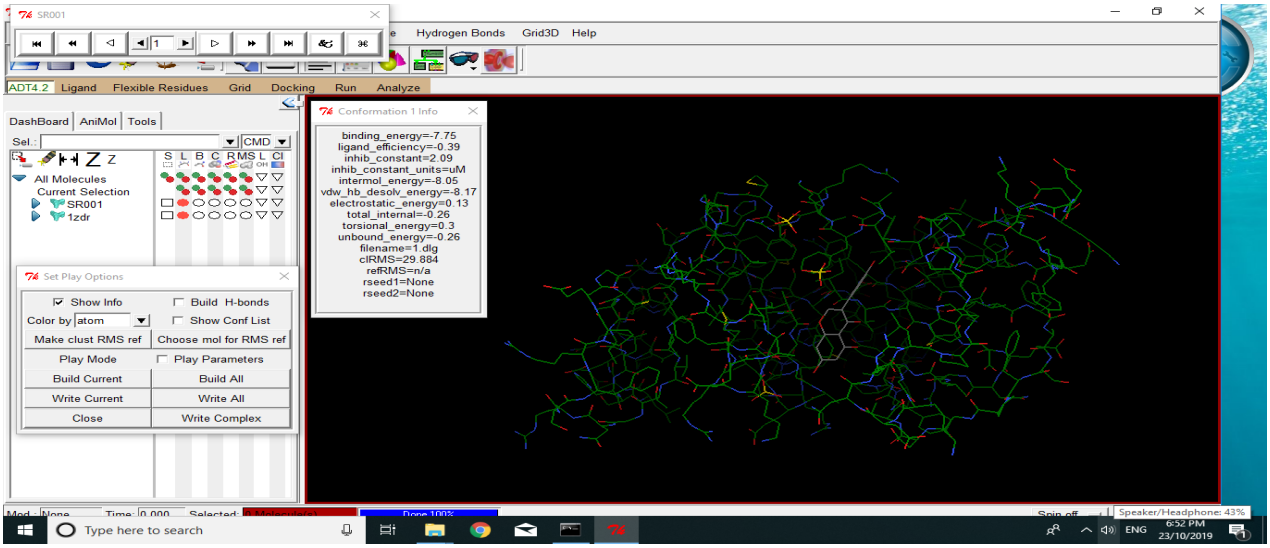
All the calculations were carried out by using Autodock 4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus.

***In-Silico* Analysis by Docking Of Genistein with Dhf Reductase**

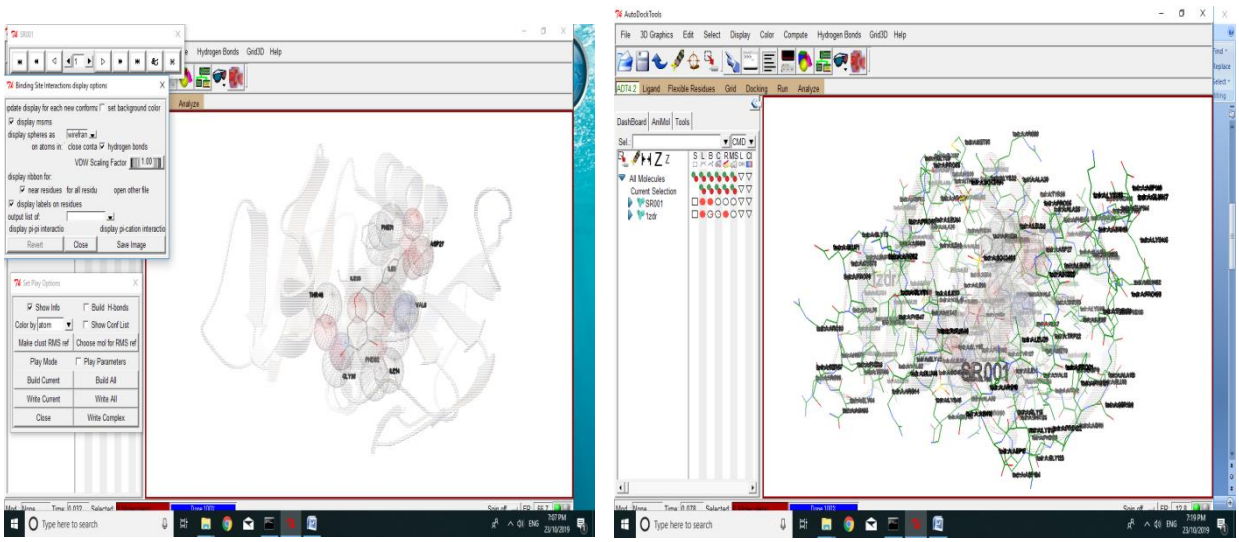
Docking was done using AutoDock 4.2; in order to assign the perfect grid of each ligand, grid box values were obtained by trial and error. 20−23 Grid maps with 60 × 60 × 60 points were made and the grid point spacing was 0.375 A.The Lamarckian genetic algorithms (LGA), considered one of the best docking methods available in AutoDock, was adopted to perform the molecular docking.

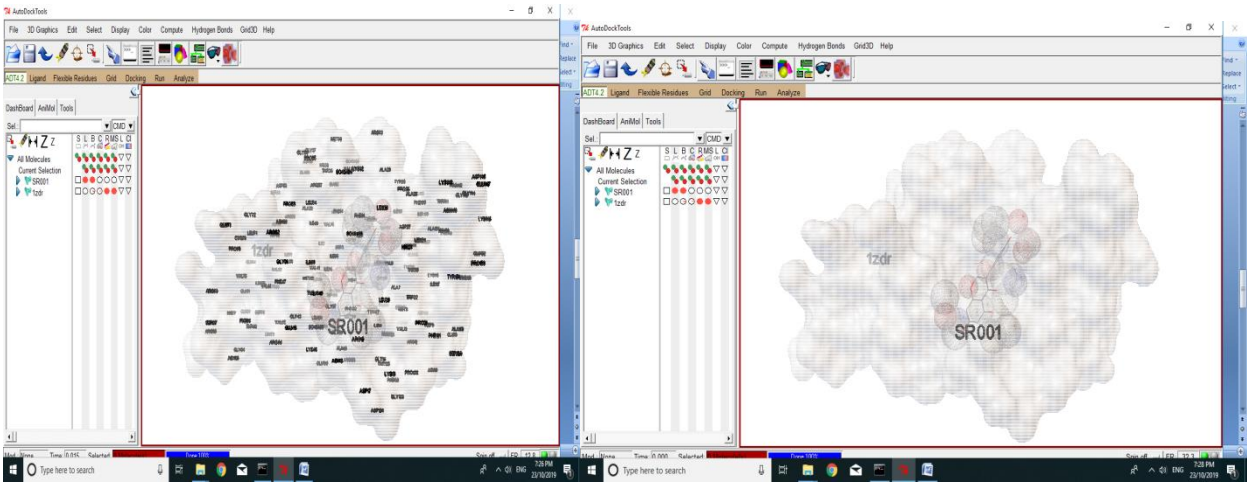


3d optimization **Genistein and DHFR**



Drug binds to receptor after conformational play

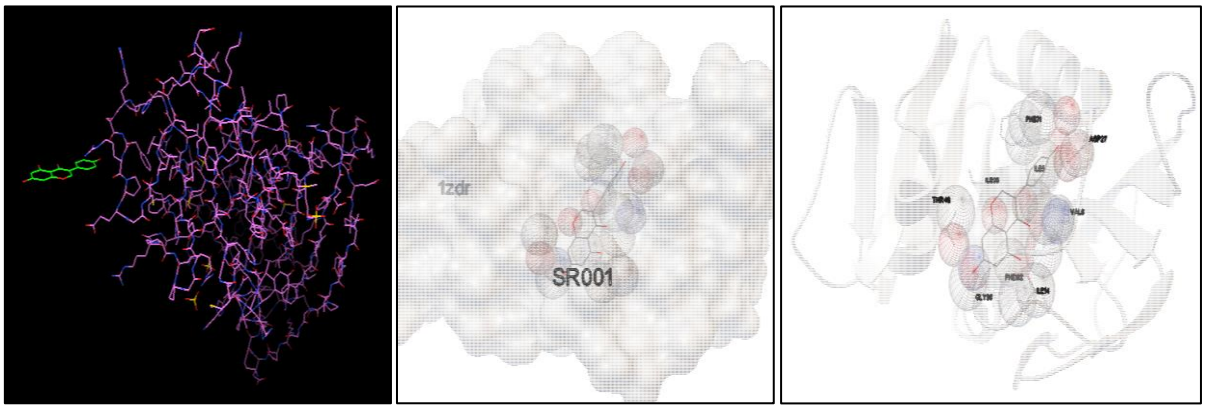




After drug interaction

Table 1. Docking conformation information

S.No.	Specifics	Array
1.	Binding Energy	-7.75
2.	Ligand_Efficiency	-0.39
3.	Inhib_constant	2.09
4.	Intermol_energy	-8.05
5.	Vdw_hb_desolv_ energy	-8.17
6.	Electrostatic_energy	0.13
7.	Torsional energy	0.3
8.	Unbound energy	-0.26
9.	cIRMS	29.884



Docking of Genistein with DHFR

RESULT AND DISCUSSION

In the present investigation, docking experimentation revealed the interaction of genistein (ligand, SR001) with DHFR (protein) PDB ID 1ZDR and residues involved in this complex (Figure 1). For such interaction studies, the most important requirement was the proper orientation and conformation of ligand, which fitted to the enzyme binding site appropriately and formed protein-ligand complex. Therefore, optimal interactions and the best autodock score were used as criteria to interpret the best conformation among the 30 conformations, generated by AutoDock program. In order to evaluate the candidature of compound genistein (SR001) as inhibitor of DHFR, in terms of their binding affinity to DHFR active site, we have performed molecular docking. The protein-ligand complex structures were suitable for the docking study, since the ligand pockets were clearly determined.The docking results are shown in Table 1. The docked compound genistein had the docking energy of -7.760 with DHFR.Docking pose of the best conformation of compound genistein (SR001) in the binding site of DHFR protein is shown in Figure 2. Vander wall interactions andhydrogen bonding plays an important role for the structure and function of biological molecules, especially for inhibition in a complex. The main amino acids involved in present study were GLY98, GLY97, THR46, ILE96, PHE102, VAL6, PHE31, ILE14, ALA7, ASP27, ILE5, and TYR30 (Figure 3). It can be inferred that the ligand has affinity for the active site and can act as competitive inhibitor.

CONCLUSION

From the above molecular docking simulation and molecular modeling studies it is concluded that the genistein acts as a potent inhibitors of DHF reductase and may act as a potent drug for the treatment of disease associated folate metabolism as it shows good binding affinity with the macromolecule with very good value of dissociation constant Ki. The genistein also strictly follows Lippinski's Rule of Five, thus having very good drug score as well as drug likeness score.

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REFERENCE

1. Ferreira, L. G., Dos Santos, R. N., Oliva, G., & Andricopulo, A. D. (2015). Molecular docking and structure-based drug design strategies. *Molecules*, *20*(7), 13384-13421.
2. Srivastava, V., Kumar, A., Mishra, B. N., & Siddiqi, M. I. (2008). Molecular docking studies on DMDP derivatives as human DHFR inhibitors. *Bioinformation*, *3*(4), 180.
3. Himesh, S., & Singhai, A.K. (2014). *In-vivo* and *In-silico* Design of Anti-inflammatory Activity of Rutin. *SGVU Int J Env Sci Technol*. 2(1), 48.
4. Ajaz, A.G., & Farooqi, H. (2015). Bioactivity of genistein: A review of in vitro and in vivo studies. *Biomedicine & Pharmacotherap, 76; 30.*
5. Spagnuolo, C., Russo, G. L., Orhan, I. E., Habtemariam, S., Daglia, M., Sureda, A., ... & Nabavi, S. M. (2015). Genistein and cancer: current status, challenges, and future directions. *Advances in nutrition*, *6*(4), 408-419.
6. Malik, J. K., Soni, H., & Singhai, A. K. (2013). QSAR-Application in Drug Design. *International Journal of Pharmaceutical Research & Allied Sciences*, *2*(1).