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**Review Article**

# Rutin as a Potent Inhibitor of Dihydrofolate Reductase: A Computational Design and Docking

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**Abstract:** Earlier the process of drug research was confined to the empirical testing of a large number of compounds for a specific activity. The bioactive phytochemical flavonoid has focused on the current scenario for various pharmacological activities. Flavonoids are chief active constituents have been used to management of various human diseases. Rutin (quercetin-3- rhamnosyl glucoside) as the flavonoids display antiviral, anticancer, anti-inflammatory, and heart disease protective activities. Rutin by acting as antioxidants exhibited several beneficial effects, such as anti-inflammatory, anti-allergic, antiviral as well as an anticancer activity. Dihydrofolate reductase (DHFR, EC 1.5.1.3) is one of the enzymes active in the folate cycle which plays a central role in DNA synthesis. DHFR Inhibition is a key element in the treatment of many diseases, including cancer and AIDS related infections. A investigate 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 rutin strictly follows Lippinski's rule of five, thus having very good drug score as well as drug likeness score. The present study reveals that rutin has good binding affinity for DHFR and this can be use for the inhibition purpose and thus good antibacterial and anti cancer activity along with other important activities could be obtained.

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

## INTRODUCTION

Molecular docking is one of the most often used methods in SBDD because of its ability to envisage, 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 energetic, providing rankings of docked compounds based on the binding affinity of ligand-receptor complexes. Molecular docking programs execute these responsibilities 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 (Ferreira, L. G. *et al.*, 2015). Inside 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 manyother compounds necessary for RNA, DNA and protein synthesis. Therefore, DHFR represents an attractive target for increasing new antibacterial & antitumor agents (Srivastava, V. *et al.*, 2008; Jitender, k. *et al.*, 2013). Flavonoid is major phenolic compounds are becoming the major subject of medical research (Himesh, S., & Singhai, A.K. 2014). The flavonoid rutin (vitamin P or rutoside) is a present in the plant

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kingdom as Allopathic substances. Rutin is the rhamnoglucoside of the flavonoid quercetin and found in many plants and used for treatment of various diseases related to the vascular. It is quercetin-3-rutinoside or 3, 3',4', 5,7-pentahydroxy flavones-3-rutinoside, and has a chemical formula $C_{27}H_{30}O_{16}$.

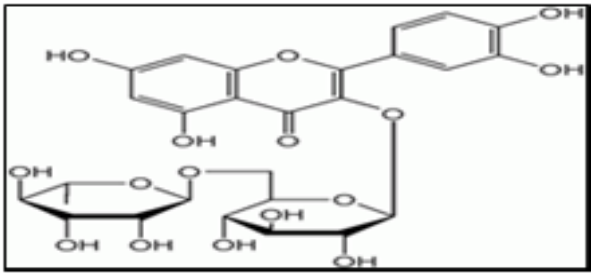

**Fig: 1 Structure of Rutin**

It has been reported that phenolic compounds show anti-microbial activity against a wide range of microorganisms. By virtue of the presence of the free phenolic groups they also acquire noteworthy anti-inflammatory activity (Himesh, S. *et al.*, 2014; Himesh, S. *et al.*, 2013 Himesh, S. *et al.*, 2018; Ganeshpurkar, A., & Saluja, A. K. 2017; Ashok, P. K., & Saini, B. 2013). Antioxidant activity of Rutin has already been reported (Himesh, S. *et al.*, 2013) and literature shows that Rutin as a ligand molecule can be potential to exhibit other pharmacological activities too. Consideration of all the aspects in literature survey an attempt had been made in study binding affinity of rutin to DHFR for development potent DHFR inhibitor which acquire various pharmacological effect.

## EXPERIMENTAL WORKS

### Procedure for Docking

To investigate the potential binding mode of Rutin (Fig 2), the compound was subjected to GA based docking using the VLife MDS docking software Biopredicta tools. The X-ray crystal structure of Dihydrofolate reductase was downloaded from the protein data bank (PDB ID: 1ZDR, Fig. 3), and was used for the docking study as receptor.

Ligand 2D structures was drawn using ACD/ChemSketch software. The structures were saved as .pdb file format for docking. The parameters like Generations was set as 400, Fitness Function Criteria as Dock Score, Translation as 2.0, and Rotation step size of 100 were set and docking process was started. The cavity with surface is shown in Fig 4.

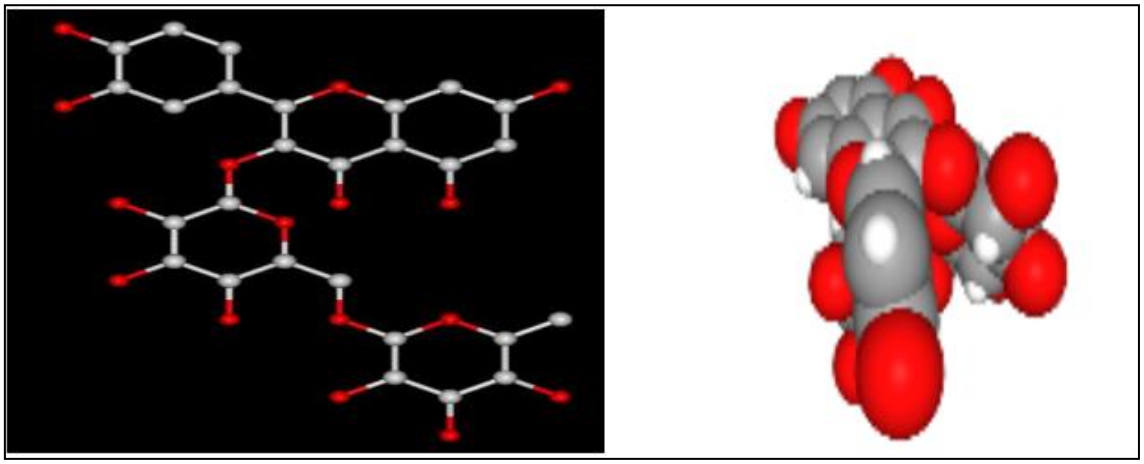

**Fig 2: Rutin structure (Ball –Stick & Space filling)**

**Fig 3:Dihydrofolate reductase DHFR (PDB ID : 1ZDR) 3D structure**

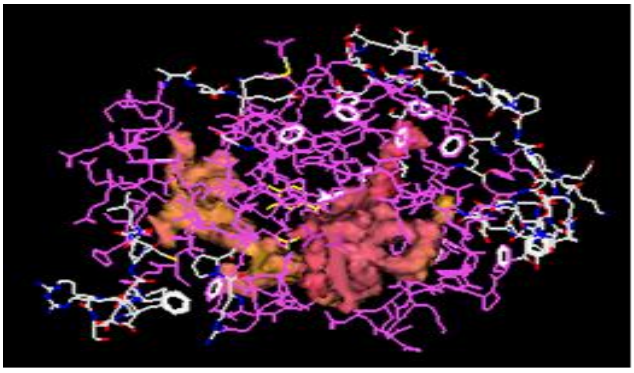

**Fig 4:Cavity volume in 1ZDR**

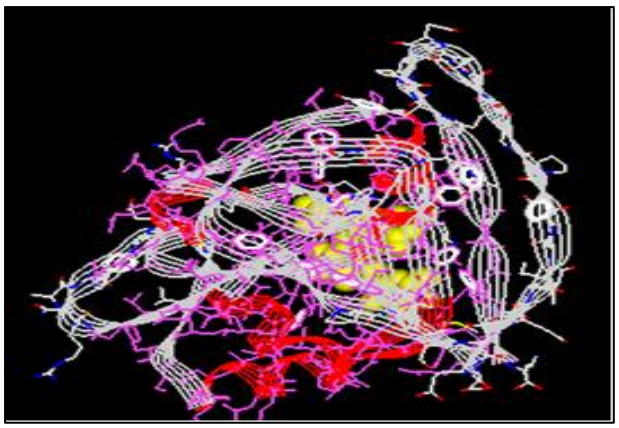

**Fig 5: Docked Complex of Rutin-1ZDR (Rutin highlighted in golden colour space filled model)**

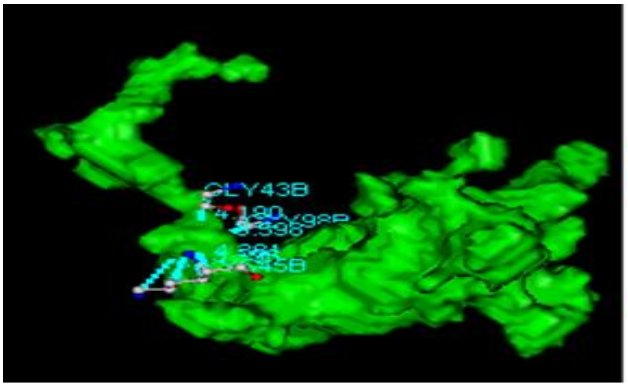


**Fig 7:Hydrophobic Interaction**

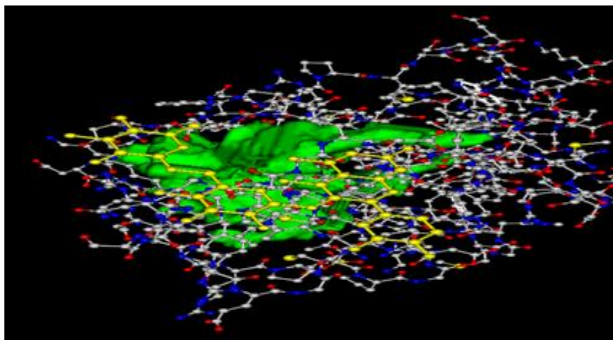

**Fig 6:Docked complex of Rutin-1ZDR**

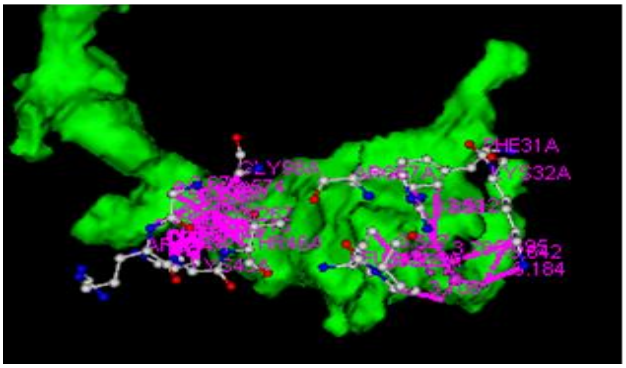


**Fig 8:Van der Waals Interaction**

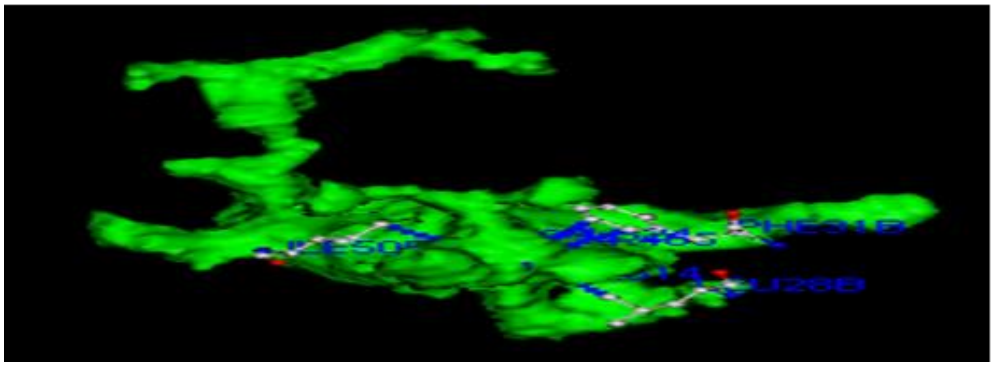

**Fig 9: Charge Interaction**

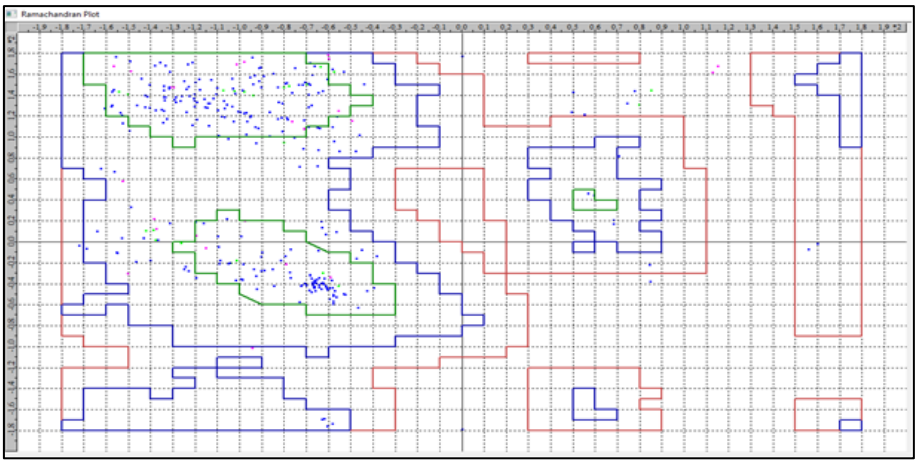

**Fig 10: Ramachandran Plot for the Rutin-1ZDR docking**

## MOLECULAR DOCKING SIMULATIONS

All the calculations were carried out by using the VLife MDS as docking tool. The visualization and other programs necessary for docking studies were performed out by means of various biopredicta docking tools available with VLife MDS software.

## RAMACHANDRAN PLOT

The core of the predicted protein structure or allowed areas in the plot showing the preferred regions for psi/phi angle pairs for residues in DHFR was determined through Ramachandran plot (Ramachandran, GN 1963).

## RESULT AND DISCUSSION

Rutin as a ligand was docked with Dihydrofolate reductase (PDB ID : 1ZDR) to evaluate the binding affinity. The docked complex showed the docking score of -8.57785. The docked complex showed number of interactions with the residue atoms with different distance but some of the most important residues such as LYS45B 1657C, GLY98B 2067C, MET1A 2625H, LEU28A 2845H, PHE31A 251C, LYS32A 261C, GLY43A 2966H, ARG44A 343N, THR46A 364C, PRO55A 439C, GLU100A 783C, LYS45B 4275H, ALA99B 4687H, LEU101B 2084N showed Van der Waals interactions, hydrophobic interaction, charge interaction and hydrogen bonding in the present docking study. These interactions play an important role for the binding affinity of ligand and receptor. Docking pose of the best conformation of compound Rutin in the binding site of DHFR protein is shown in Fig 5 and 6. The main interactions with atom residue are shown in table 1. Hydrophobic interactions observed in docking of Rutin and 1ZDR is shown in Fig 7 and Van der Waals interactions are shown in Fig 8 while Fig 9 shows charge interactions. The Ramachandran plot (Fig 10) revealed the phi-psi torsion angles for all residues in the structure except those at the chain termini. The darkest areas communicate to the core regions representing the most favorable combinations of phi-psi values. The present study reveals that Rutin has good binding affinity for DHFR and this can be used for the inhibition purpose and thus virtuous antibacterial and anti cancer activity along with other important activities could be obtained.

## CONCLUSION

From the above molecular docking simulation studies it is concluded that Rutin acts as a potent inhibitors of DHF reductase and may act as a novel 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 rutin also strictly follows Lippinski's Rule of Five, thus having very good drug score as well as drug likeness score. Rutin by performance as antioxidants exhibited several beneficial effects, such as anti-inflammatory, antiallergic, antiviral as well as an anticancer activity. By molecular docking approach rutin showed well-intentioned binding affinity for DHFR, thus act as inhibitor of DHFR.

## ACKNOWLEDGEMENT

Authors are thankful to VLife Sciences for providing the molecular modeling and docking software.

**Table 1. Docking Interactions**

| | |
|---|---|
| LYS32A 2881H | HYDROGENBOND_INTERACTION |
| ARG44A 343N | HYDROGENBOND_INTERACTION |
| THR46A 2997H | HYDROGENBOND_INTERACTION |
| GLU100B 4692H | HYDROGENBOND_INTERACTION |
| GLY43B 1636C | HYDROPHOBIC_INTERACTION |
| LYS45B 1657C | HYDROPHOBIC_INTERACTION |
| GLY98B 2067C | HYDROPHOBIC_INTERACTION |
| MET1A 2625H | VDW_INTERACTION |
| LEU28A 2845H | VDW_INTERACTION |
| PHE31A 251C | VDW_INTERACTION |
| LYS32A 261C | VDW_INTERACTION |
| GLY43A 2966H | VDW_INTERACTION |
| ARG44A 343N | VDW_INTERACTION |
| THR46A 364C | VDW_INTERACTION |
| PRO55A 439C | VDW_INTERACTION |
| GLU100A 783C | VDW_INTERACTION |
| LYS45B 4275H | VDW_INTERACTION |
| ALA99B 4687H | VDW_INTERACTION |
| LEU101B 2084N | VDW_INTERACTION |

**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. Jitender, k., Malik, H.S., Singhai, A.K., & Harish,P. (2013). QSAR- Application in Drug Design. IJPRAS. *2(1), 1-13.*
4. 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.*
5. Himesh, S., Jitender, M., Sandeliya,P., & Singhai, A.K. (2014). In- silico analysis to access the antibacterial effect of Rutin on E.coli: molecular docking approach. *UJP, 03 (06), 23-29.*
6. Himesh, S., Singhai, A.K., Malik, J.k., & Sharma,S. (2013). Antimicrobial and Anti-inflammatory Activity of the Hydrogels Containing Rutin Delivery. *Asian Journal of Chemistry; 25(15), 8371.*
7. Himesh, S., Malik, J., Yadav, A.P., & Yadav,B. (2018). Characterization of Rutin isolated by leaves Annona squamosa by Modern Analytical Techniques. *EJBPS, 5; 6 ,484-489.*
8. Ganeshpurkar, A., & Saluja, A. K. (2017). The pharmacological potential of rutin. *Saudi pharmaceutical journal*, *25*(2), 149-164.
9. Ashok, P. K., & Saini, B. (2013). HPLC analysis and isolation of rutin from stem bark of Ginkgo Biloba L. *Journal of Pharmacognosy and Phytochemistry*, *2*(4).
10. Ramachandran, GN (1963) .Stereochemistry of polypeptide chain configurations.J. *Mol. Biol.*