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Potential antibacterial drug targets for Quercetin and Rutin: An *in silico* study using AutoDock

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ABSTRACT

In this study, we analysed the possible antibacterial drug target and mode of action of quercetin and rutin against Staphylococcus aureus. These flavonoid compounds commonly found in many plants and trees are well known for its antibacterial activity. Eight protein molecules from S.aureus, belonging to various pathways to its cell survivability were chosen. These protein molecules were docked with quercetin and rutin to find the most significant protein target. Quercetin exhibited lowest binding energy of -8.48 Kcal/Mol and Ki value of 605.86 nM against Isoleucyl tRNA Synthetase (IleRS). Rutin exhibited lowest binding energy of -8.72 Kcal/Mol and Ki value of 405.34 nM against Dihydro Folate Reductase (DHFR). This study suggests that the possible mode of action of quercetin is preventing protein synthesis by inhibiting IleRS and possible mode of action of rutin is preventing folic acid synthesis in S.aureus by inhibiting DHFR. This study opens up opportunity for further research on these natural compounds, as it is evident that, these compounds have potential to be used as lead molecules in drug development. These flavonoid compounds need further in vitro study before confirmation of its mechanism of action.

Keywords: Quercetin, Rutin, *Staphylococcus aureus*, AutoDock, PatchDock

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INTRODUCTION

Staphylococcus aureus is a gram positive bacteria and its diameter ranges from 0.5 µm to 1.5 µm. It is a non motile, non spore forming facultative anaerobes. It is a commensal which could be found in the nasopharynx and skin in the human body. It is capable of causing infection in immunologically compromised patients in the hospital and also in the healthy individuals outside the hospital in various communities. The usual spot of infection in humans was found to be gastro intestinal tract, vagina, urethra, nose and skin [1]. The infection rate due to *Staphylococcus aureus* is increasing steadily [2]. The main challenge in treating Staphylococcus aureus related infection is tackling of resistance posed by the bacteria due to the use of drugs repeatedly [3, 4]. So researchers are on the pursuit of natural compounds to tackle the resistance offered by the *S.aureus*.

Flavanoids have been identified to be a great alternative to combat multi drug resistance in the treatment of infectious disease. These flavonoids could be obtained from natural sources like fruits, vegetables, etc. Quercetin and rutin , two of some of the well known flavonoids, were reported to have anti bacterial activity against Staphylococcus aureus. The molecular formula of quercetin and rutin are C15H10O7 and C27H30O16 respectively. In addition to their antibacterial activity, they are reported to have anti fungal, anti viral and anti cancer activity as well [5, 6, 7, 8, 9].

The drug targets chosen belongs to one of the following biological role i) Cell wall synthesis; ii) Protein synthesis; iii) Nucleic acid synthesis; and iv) Cell metabolism. PBP1b and transglycosylase are essential for cell wall biosynthesis. Transglycosylase catalyses the formation of linear glycan chain and PBP1b is responsible for formation of peptide cross link between the glycan strands. These two proteins are well known drug targets for many reported drugs [10-12]. Isoleucyl tRNA synthetase (IleRS) is one of the essential proteins for synthesising proteins.

It facilitates the joining of isoleucine to tRNA at the active site and is responsible for the hydrolysation of incorrectly acylated amino acids at its editing active site. Inhibiting IleRS blocks protein synthesis [13]. DNAG-type primase, DNA gyrase, DNA topoisomerase 4 are essential for nucleic acid synthesis. DNAG-type primase is essential for primer synthesis and serves as an important enzyme for DNA replication. DNA gyrase is also known as DNA Topoisomerase 2 and is essential for the ATP dependent negative super coiling of closed circular DNA. DNA Topoisomerase 4 is a homolog of DNA Gyrase. Both perform the same function but differ in their mode of action with DNA Gyrase wrapping DNA around itself whereas the topoisomerase does not wrap DNA around itself [14, 15]. Dihydropteroate synthetase (DHPS) and DiHydro Folate Reductase (DHFR) are the proteins essential for folic acid synthesis. Folic acid is essential for the synthesis of nitrogen bases purine and pyrimidine [16, 17].

MATERIALS AND METHODS

3D structures of the macromolecules were downloaded from RCSB PDB website (http://www.rcsb.org/pdb) with the following PDB ID: 2Y2I, 3VMR, 1FFY, 4E2K, 3G75, 2INR, 4FGG, 1AD1.

The ligands molecules Rutin (PubChem ID: 5280805) and Quercetin (PubChem ID: 5280343) were downloaded from the PubChem website (http://pubchem.ncbi.nlm.nih.gov).

Meta pocket analysis was done to identify the best binding sites in the target proteins [18, 19]. AutoDock 4.2.1 and PatchDock webserver were used to perform the protein-ligand dockings [20-23].

PyMOL and LigPlus softwares were used to analyse the docking results obtained from AutoDock and PatchDock [24, 25].

RESULTS

The AutoDock and PatchDock analysis of Quercetin with the chosen protein targets are given in Table.1 and Table.2. Quercetin demonstrated highest affinity towards Isoleucyl tRNA Synthetase (IleRS) both in AutoDock and PatchDock. In PatchDock, an ACE value of -331.04 Kcal/Mol and in AutoDock, a free binding energy of -8.48 Kcal/Mol and Ki value of 605.86 nM was observed for IleRS. Quercetin formed 4 hydrogen bonds with Lys-260 (2.3Å; 2.0Å), Asn-257 (1.9Å) and Lys-279 (2.3Å). As shown in Figure.1.

Table.1: AutoDock results of Quercetin against the chosen drug targets

Target proteins	Binding energy (Kcal/Mol)	Inhibition constant	No. of Hydrogen bonds
Isoleucyl tRNA Synthetase	-8.48	605.86 nm	4
Dihydropteroate synthetase	-7.78	1.97 µm	5
Transglycosylase	-7.23	5.02 µm	3
DNAG	-7.07	6.63 µm	4
DHFR	-7.04	6.88 µm	5
DNA Topoisomerase 4	-6.21	28.18 µm	5
DNA Gyrase	-6.07	35.65 µm	5
PBP1b	-5.57	83.14 µm	4

Table.2: Patchdock score for Quercetin against the protein drug targets

Target protein	Patch dock score	Atomic Contact Energy (Kcal/Mol)
Isoleucyl tRNA synthetase	4626	-331.04
DHFR	3330	-275.41
DNA Topoisomerase 4	3474	-266.33
PBP1b	3276	-211.23
DNAG	3390	-206.26
DHPS	3470	-196.30
Transglycosylase	3750	-192.87
DNA Gyrase	3476	-174.34

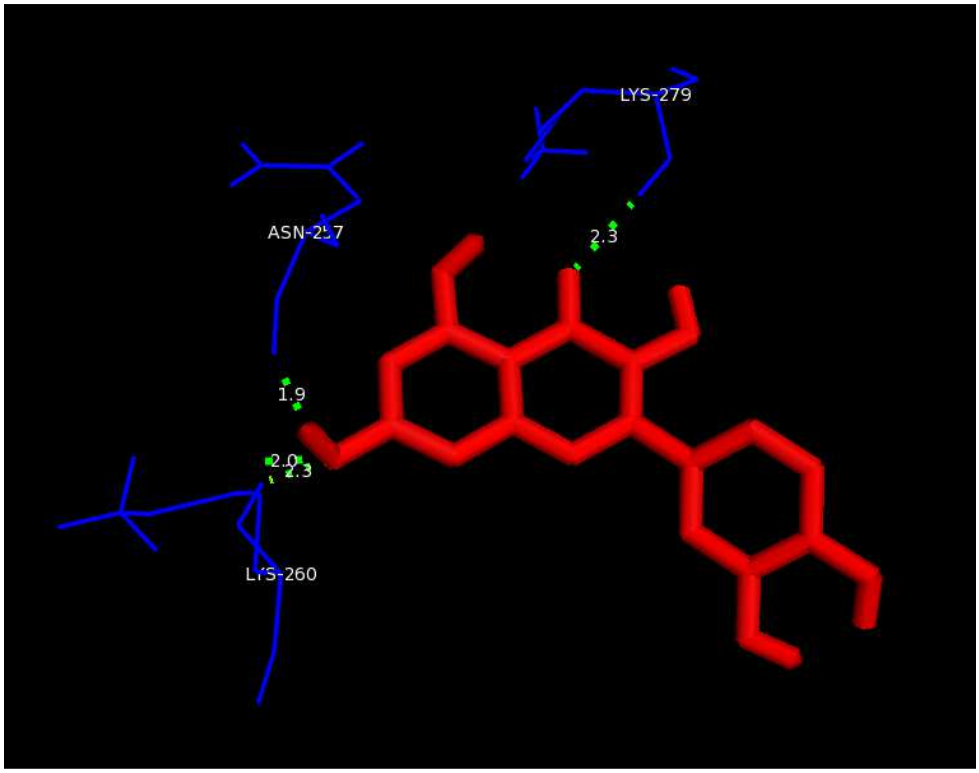

Figure.1: Interaction of quercetin and IleRS (PyMOL)

AutoDock and PatchDock analysis demonstrated that, rutin had highest significance to Dihydrofolate Reductase (DHFR). PatchDock gave a highest ACE value of -414.31 Kcal/Mol. AutoDock displayed a free binding energy of -8.72 Kcal/Mol with Ki value of 405.34 nM. Quercetin formed 10 hydrogen bonds with DHFR, Leu-5 (1.8Å), Asp-27 (2.1Å, 2.8Å, 2.0Å), Leu-24 (2.2Å, 2.3Å, 2.1Å), His-23 (2.5Å), Trp-22 (2.4Å) and Leu-20 (1.8Å) as shown in Figure.2.

Table.3: AutoDock results of Rutin against the chosen drug targets

Target protein	Binding energy (Kcal/Mol)	Inhibition constant	No. of Hydrogen bonds
DHFR	-8.72	405.34 nm	10
PBP1b	-7.51	3.12 µm	11
DNAG	-6.53	16.28 µm	11
Transglycosylase	-6.18	29.47 µm	5
Isoleucyl tRNA Synthetase	-4.51	493.74 µm	11
DNA Topoisomerase 4	-4.17	880.17 µm	5
DNA Gyrase	-3.18	4.66 mm	8
DHPS	-3.14	5.0 mm	7

Table.4: Patchdock score for Rutin against the protein drug targets

Target protein	Patch dock score	Atomic Contact Energy
DHFR	5036	-414.31
DNA Topoisomerase 4	4520	-358.75
Transglycosylase	5130	-351.47
PBP1b	4972	-280.7
DNAG	4642	-252.03
DNA Gyrase	4354	-229.27
Isoleucyl tRNA Synthetase	5362	-191.71
DHPS	4952	-156.9

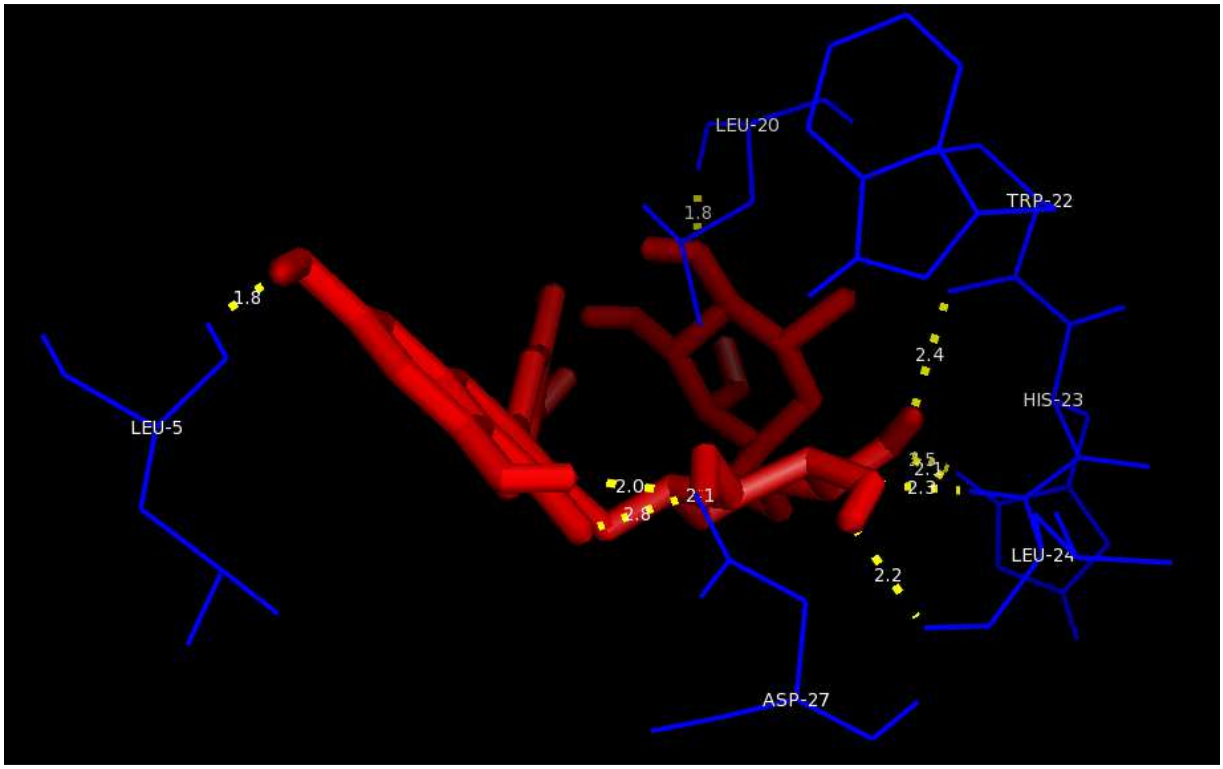

Figure.2: Interactions between rutin and DHFR (PyMOL)

DISCUSSION

Quercetin a well known flavaonol compound and rutin another well known flavonoid compound that is a glycoside of quercetin and rutinose are the key flavonoid compounds analysed in this study. These flavonoids have been studied earlier by Basile et al 2000 for their antibacterial activity, against a wide range of bacterial pathogens, such as; *E. coli, K. pneumonia, E. aerogenes, S. aureus, P. vulgaris, P. aeruginosa* and *E. cloacae.* Here in this study, we focused on *S. aureus*, due to the promising activity demonstrated by these flavonoid compounds. Quercetin and rutin demonstrated an MIC value of 16µg and 32µg respectively, against *S.aureus*, as reported by Basile et al 2000. Though, the promising activity of these natural compounds has been reported, the potential mechanism of action of these molecules has not been discussed. Hence, here in this in-silico analysis, we have analysed the possible mode of action of these molecules in regards to anti *S. aureus* activity.

The results from this study suggests that, quercetin could potentially inhibit Isoleucyl tRNA Synthetase protein in *S. aureus* and rutin could potentially inhibit Dihydrofolate Reductase protein in *S. aureus.* This leads to the hypothesis that, Quercetin inhibits protein synthesis in *S. aureus* and Rutin inhibits folic acid synthesis in *S. aureus.* Although this study needs further in-vitro data support, it sets a good guidance for scholars working on these molecules and also provides a new protein target set for studying the anti-bacterial activity in-silico.

CONCLUSION

This study was done to support and analyse the antibacterial activity of quercetin and rutin against *S.aureus*. As reported by Basile et.al 2000, quercetin and rutin posses good antibacterial activity. But the mode of action of the molecules is unclear. In this in-silico analysis, the possible mode of action of these flavonoid molecules were identified. Proposed mechanism of action of quercetin and rutin is by preventing protein synthesis and folic acid synthesis respectively. These identifications need further in-vitro validation before confirmation.

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