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**RESEARCH ARTICLE**

# Exploring the 5-lipoxygenase inhibitory potentials of gossypetin 8-glucuronide through *in silico* approach

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## ABSTRACT

On searching several life sciences directories and numerous pharmaceutical databases (PubMed, Google Scholar, etc.) regarding the possible anti-inflammatory roles of gossypetin, it was found that not much effort has been devoted by the global researchers with deep insights into the therapeutic targets such as COX-1, COX-2, 5-lipoxygenase (5-LOX), PLA2, TXA2, and PGDH. Inspiring from this fact, an initial exploration of inhibitory potentials of gossypetin (in the form of gossypetin 8-glucuronide) against an inflammatory target, 5-LOX was performed using the induced-fit molecular docking approach by employing the Glide module of the Schrodinger (Maestro 9.1) software. The dock poses revealed that the hydroxyl (-OH) group (referred to as 4'-hydroxy) situated on the aromatic ring attached with the 5-hydroxy-4*H*-chromen-4-one scaffold formed a single hydrogen bonding with the negatively charged amino acid residue Asp766 and demonstrated an impressive Glide docking score of –9.112 kcal/mol. This study will motivate the modern researchers of diverse backgrounds for the further explorations pertaining to the multifarious roles, molecular mechanism(s), interactions, applications, etc.

**Keywords:** Anti-inflammatory, Docking, Gossypetin, Inhibitor, *In silico*, Lipoxygenase

## INTRODUCTION

Gossypetin, the plant metabolite, was first isolated in the year 1899 from *Gossypium herbaceum* (Indian Cotton Plant) by the researcher named Perkin.[1] It is a hexahydroxyflavone where the hydroxyl groups situated at the 3-position, 3'-position, 4'-position, 5-position, 7-position, and 8-position. Therefore, it is also known as 3,5,7,8,3',4'-hexahydroxyflavone among the researchers.[2] It is the conjugate acid of gossypetin(1-) and gossypetin-3-olate. This 7-hydroxyflavonol exists mainly diverse forms in nature such as gossypetin 8-*O*-glucoside, gossypetin-3-*O*-*β*-*D*-robinobioside, gossypetin-3-*β*-*D*-(2-*O*-*β*-*D*-glucopyranosidoglucopyranoside)-8-*β*-*D*-glucopyranoside, and gossypetin 8-*O*-rhamnoside.[3] It is primarily isolated from *Hibiscus sabdariffa* (Family: Malvaceae) calyx and flowers.[4] This phytoconstituent is principally isolated from this plant for pharmacotherapeutic applications after modern-day explorers reported that it exhibits multiple pharmacological activities such as cytoprotective, anti-atherosclerotic, anti-microbial, anti-mutagenic, anti-oxidant, anti-proliferative, and radioprotective.[5] To meet the high global market demand for this product at present, it is exclusively manufactured through well-established economic synthetic routes.[6]

However, on searching several life sciences directories and numerous pharmaceutical databases (PubMed, Google Scholar, etc.) regarding the possible anti-inflammatory roles of gossypetin, it

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was found that not much effort has been devoted by the global researchers with deep insights into the therapeutic targets such as COX-1, COX-2, 5-lipoxygenase (5-LOX), PLA2, TXA2, and PGDH. Inspiring from this fact, an initial exploration of inhibitory potentials of gossypetin 8-glucuronide IUPAC name: 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-8-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl) oxy)-4*H*-chromen-4-one [Figure 1] against an inflammatory target, 5-LOX was performed using the induced-fit molecular docking approach by employing the Glide module of the Schrodinger (Maestro 9.1) software.

## MATERIALS AND METHODS

### Sketching of ligands

The ligands were illustrated in a 2D-format originally by making the use of ChemDraw® v.8.0 software, and further, the ChemDraw file was immediately saved into the folder in the form of .cdx format. Later, the file was saved into the mol format for importing it into the software. The LigPrep module was exploited for amending the torsion of the ligand structures. An accurate protonation order was approved for the docking function. For each ligand at a pH of 7.0 ± 2.0, a detailed sum of stereochemical states was assigned, keeping 1.0 as the dielectric constant. The 3D-structure of the ligand was additionally desalted, tautomerized further, and in due course, OPLS_2005 force field was employed for the optimization.[7,8]

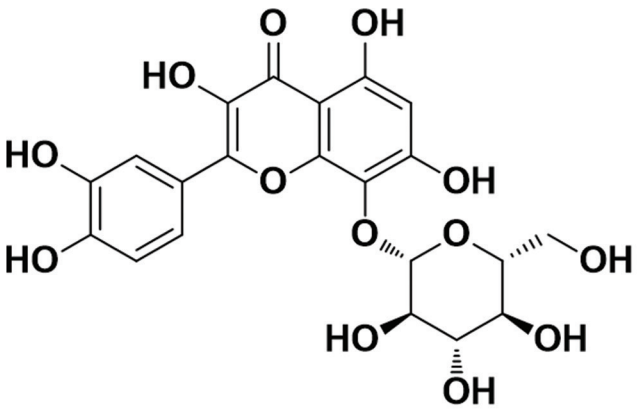


**Figure 1:** Molecular structure of gossypetin 8-glucuronide

### Preparation and validation of protein targets

For the needy purpose of drug discovery, the protein structure of the 5-LOX was downloaded as protein data bank (PDB) ID: 6VSB from the PDB. For organizing the biological structure of the 5-LOX for the docking studies with gossypetin 8-glucuronide, subsequent pre-processing was carried out: All aqueous elements were taken away ahead of 5A° distance; the hetero group, metal ions, and cofactors were eliminated; and proper formal charges and bond orders were duly allocated. The hydrogen-bonding networks and hydrogen atoms were optimized by making use of the H-bond assignment tool and Impref utility tool. The receptor grid was approximated for the 5-LOX target, where the ligands combine at the predicted active site. The grid was formed in a manner that it lies in the centroid of the ligand and close up the whole ligand. The Van der Waals scale factor was set at 1.0 and the charge cut off was set at 0.25. The energy-minimization of poses was performed for the ligands and the study was performed through induced-fit docking (IFD) through XP-mode.[9,10]

### Molecular docking studies

Based on the computational method, the induced-fit molecular docking (IFD) exploration engages the applications of the structure-based drug design technique. The free-state ligand's 3D-structure (comprising a distinct geometry) was effectively docked with a previously recognized macromolecular protein (biological target) at its active site. The binding of the ligand with the target site was predicted based on the considered quality of the fit. The system (Glide module of Schrodinger software) computes the low-energy assessment on the basis of the proper interfaces. Each has its individual allusions based on the purpose of reasonable steric clashes. For the execution of the plausible interactions, the following considerations were taken: (a) 0.18 A° was set as the RMSD cut off value was fixed; (b) confining the ligand poses numbers to 20; (c) setting the Van der Waals scaling value to 0.5 for the ligand and 0.7 for the receptor; and (d) side chains minimization. The glide score was estimated for every ligand, and

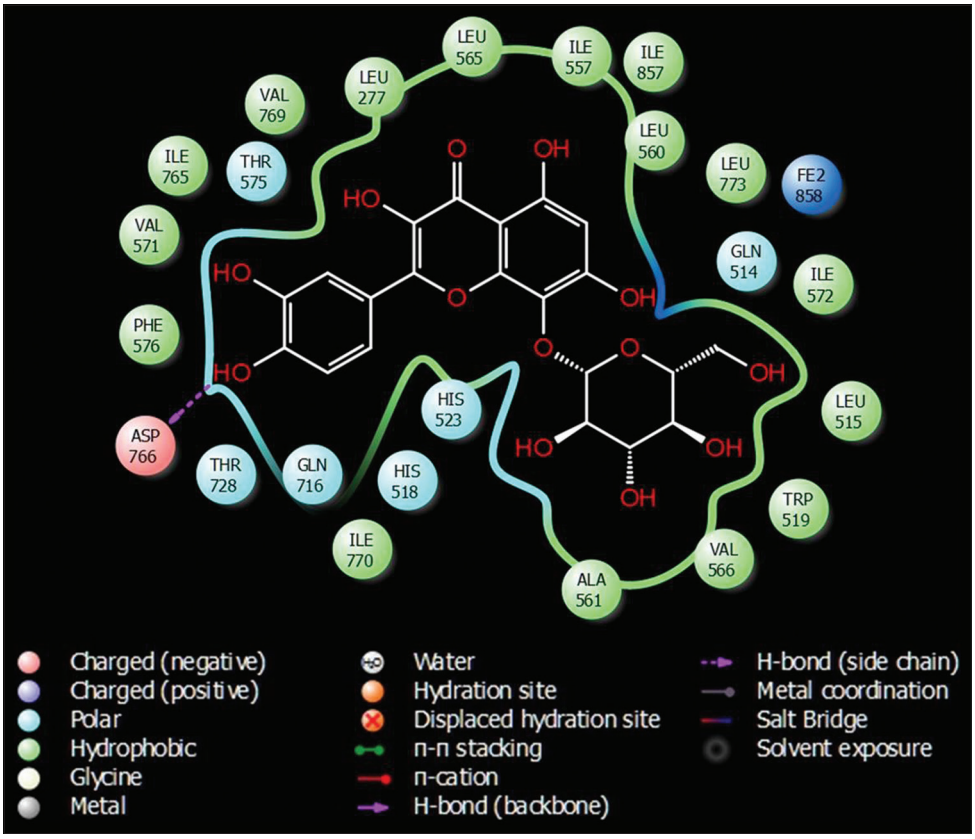


**Figure 2:** Docking pose of gossypetin 8-glucuronide as an inhibitor of 5-lipoxygenase enzyme (PDB ID: 1N8Q)

based on the attained biological data, the ligands were graded.[11,12]

## RESULTS AND DISCUSSION

The *in silico* investigation demonstrated brilliant inhibition of the inflammatory enzyme; 5-LOX by the natural phytoconstituent gossypetin with an impressive Glide docking score of –9.112 kcal/mol. The dock poses revealed that the electro-positive hydroxyl (-OH) group (referred to as 4'-hydroxy) situated on the aromatic ring attached to the 5-hydroxy-4*H*-chromen-4-one scaffold formed a single hydrogen bonding with the negatively charged amino acid residue Asp766 [Figure 2]. The compound aligned perfectly and perfectly accommodated into the "U" shaped hydrophobic cavity, where the overall active site cavity does not change significantly. In addition to it, the role of Van der Waals contacts in stabilizing the docking complex and also supports the binding of the inhibitor was determined to be 1031. However, no n-n stacking, metal coordination, and n-cation were observed from the obtained docking pose. The glucoside portion of the molecule has no interactive functions and is primarily of pharmacokinetic importance. Overall, it can be believed from this computational study that the compound exhibited a good binding affinity owing to diverse interactive forces such as hydrogen bonding, hydrophobic forces, hydrophilic forces, electrostatic charges, and steric aspects.

## CONCLUSION

This interesting computational-based investigative study has opened the anti-inflammatory perspectives of gossypetin 8-glucuronide by selectively inhibiting the enzyme target 5-LOX as evidenced by the docking pose as well as the impressive docking score. In addition to it, the *in silico* study will serve as a prototype for miscellaneous anti-inflammatory explorations against other inflammatory targets such as COX-1, COX-2, 5-LOX, PLA2, TXA2, and PGDH. Ultimately, this study will motivate the modern researchers of diverse backgrounds for the

further explorations pertaining to the multifarious roles, molecular mechanism(s), interactions, applications, etc.

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