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Quercetin, a Phytochemical Reported in Chenopodium album L.: Molecular Docking and Molecular Dynamics Simulation to Investigate Its Interaction with NUDT5

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ABSTRACT

Nudix hydrolase 5 (NUDT5) has emerged as a potential therapeutic target in breast cancer because of its roles in hormone-dependent signaling, chromatin regulation, and cellular proliferation. Quercetin, a naturally occurring flavonoid reported in *Chenopodium album* L., has structural features that may favor interaction with protein-binding sites. This study aimed to investigate the predicted binding interaction between quercetin and NUDT5 by molecular docking, and to establish a computational framework for further evaluation by molecular dynamics (MD) simulation and binding free-energy estimation. Molecular docking was performed using AutoDock Vina. The predicted binding poses were evaluated on the basis of docking scores and root mean square deviation (RMSD) values. Nine docking poses were obtained, with predicted binding affinities ranging from −8.15 to −9.19 kcal/mol. The highest-ranked pose had a docking score of -9.19 kcal/mol, indicating a favorable predicted interaction with the NUDT5 binding pocket. Particular attention was given to the functionally relevant residues Trp28A, Arg51A, Trp46B, and Glu47B, which contribute to ligand recognition within the dimeric NUDT5 structure. These findings support the computational plausibility of quercetin binding to NUDT5 and provide a basis for further investigation of the complex by MD simulations and binding free-energy calculations. However, docking scores alone cannot establish enzyme inhibition, target selectivity, or anticancer efficacy. Experimental validation through biochemical assays and appropriate breast cancer models is required to determine the functional significance of the predicted interaction.

Introduction

Cancer remains a major global health challenge, and the identification of molecular targets involved in cellular metabolism, transcriptional regulation, and tumor progression continues to be an important area of biomedical research (Martínez et al., 2021). Breast cancer is a heterogeneous disease characterized by molecular diversity, variable therapeutic responses, and the development of resistance to established treatments. These challenges have stimulated research into proteins that regulate tumor-associated metabolism and hormone-dependent signaling as potential therapeutic targets (Carvalho et al., 2025).

Nudix hydrolase 5 (NUDT5), also known as NUDIX5, belongs to the Nudix family of enzymes involved in the hydrolysis of nucleoside diphosphates linked to

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other molecular groups. NUDT5 participates in ADP-ribose metabolism and has been implicated in hormone-dependent nuclear ATP production, chromatin remodeling, gene regulation, and proliferation in breast cancer cells (Maillard et al., 2025). Page et al. demonstrated that targeted NUDT5 inhibitors can interfere with hormone-dependent signaling and cellular proliferation, establishing the biological relevance of this enzyme as a potential therapeutic target (Page et al., 2018). Nevertheless, the identification of compounds capable of selectively modulating NUDT5 remains an important research objective. The structural characteristics of NUDT5 provide a basis for computational inhibitor discovery. The enzyme functions as a dimer, and its substrate-binding pocket includes contributions from both protein subunits (Maillard et al., 2025). Structural investigations have highlighted the importance of Trp28 and Arg51 in chain A and Trp46 and Glu47 in chain B for inhibitor recognition (Almansour, 2025). These residues participate in aromatic stacking and hydrogen-bond interactions that contribute to ligand stabilization within the binding cavity (Page et al. 2018). Consequently, a computational investigation of a candidate ligand should account for the dimeric organization of NUDT5 and examine interactions across the complete binding site.

Natural products are important sources of structurally diverse molecules for pharmacological investigation (Verma et al., 2020). Quercetin is a flavonol widely distributed in edible plants and has been investigated for its antioxidant, anti-inflammatory, and cancer-associated biological activities (Asgharian et al., 2022). Its polyhydroxylated structure provides several potential hydrogen-bond donor and acceptor sites, while its aromatic ring system can contribute to hydrophobic and aromatic interactions with proteins. However, these structural features do not independently establish target selectivity, inhibitory activity, or therapeutic efficacy (Xue et al., 2025).

Chenopodium album L., commonly known as Bathua, is an edible plant widely consumed in South Asia. Its phytochemical composition includes flavonoids and other secondary metabolites of potential pharmacological interest (Verma et al., 2020). Arora and Itankar (2018) investigated the extraction, isolation, and characterization of flavonoids from the aerial parts of *C. album*. Using chromatographic separation and spectroscopic techniques, the authors identified an isolated flavonoid as quercetin. This finding supports the inclusion of *C. album* as a reported botanical source relevant to quercetin research. However, the presence of quercetin in this species does not establish that the biological effects of the whole plant are mediated exclusively by this compound (Gligorić et al., 2025)

Molecular docking predicts a plausible ligand-binding orientation, but its scoring functions have limitations in describing protein flexibility, solvent effects, and conformational changes (Zhang et al., 2024). Molecular dynamics simulation provides a complementary approach by examining the temporal behavior of a protein–ligand complex under specified physicochemical conditions. Analyses of root mean square deviation (RMSD), root mean square fluctuation (RMSF), hydrogen-bond occupancy, radius of gyration, and solvent-accessible surface area can provide information about structural stability and interaction persistence. End-point binding free-energy calculations may further support the interpretation of predicted binding behavior, although their estimates remain dependent on the computational method and sampling quality (Zafar et al., 2025). Considering the reported occurrence of quercetin in *C. album*, the biological relevance of NUDT5, and the need to evaluate ligand dynamics beyond docking, the present study was designed to investigate the predicted interaction between quercetin and NUDT5 using molecular docking and molecular dynamics simulation. The study was intended to provide additional dynamic evidence concerning the predicted quercetin NUDT5 interaction. Any implications for NUDT5 inhibition or breast cancer treatment would require independent experimental validation.

Materials and Methods

Study design

The investigation was designed as a computational molecular interaction study comprising protein structure retrieval, ligand preparation, molecular docking, docking validation, molecular dynamics simulation, trajectory analysis, and binding free-energy estimation. Quercetin was treated as an individual chemical compound reported in *C. album*. Unless quercetin was independently extracted and chemically characterized as part of the investigation, the plant was not considered the experimental source of the ligand used in the computational workflow.

The computational procedure, software versions, parameters, and analysis settings were to be documented to enable reproducibility.

Retrieval and preparation of the NUDT5 structure

The three-dimensional structure of human NUDT5 was obtained from the Protein Data Bank (PDB). The structure associated with PDB identifier 5NWH was selected as a candidate receptor structure because of its relevance to structural investigation of NUDT5 inhibitor binding.

The suitability of the selected entry was to be verified from its current PDB record, including its resolution, protein chains, bound ligand, and structural completeness. The protein structure was inspected for missing residues, alternate conformations, unresolved regions, crystallographic water molecules, ions, cofactors, and the co-crystallized ligand. The biological assembly and functional dimer were considered when defining the ligand-binding pocket because residues from both subunits can contribute to inhibitor recognition. The co-crystallized ligand was retained for binding-site identification and subsequent redocking validation. Protein preparation included the assignment of hydrogen atoms and appropriate protonation states at the selected simulation pH. Any structural modifications, including the removal or retention of water molecules and non-protein components, were documented. The selected receptor structure was examined to confirm that the binding pocket was sufficiently resolved for the intended docking analysis. If a different PDB entry was ultimately used, its identifier and justification were to be reported explicitly.

Quercetin retrieval and preparation

The chemical structure of quercetin was retrieved from PubChem using its verified chemical identity. A three-dimensional ligand structure was generated and geometry optimized using an appropriate molecular mechanics force field, such as MMFF94. The optimized structure was converted into the format required by the selected docking software. Ligand preparation included the assignment of atom types, charges, and rotatable bonds according to the requirements of the docking method. The ligand identity and preparation parameters were recorded to ensure that the compound used for docking corresponded to quercetin rather than a glycosylated quercetin derivative or another flavonoid.

Molecular docking

Molecular docking was performed to predict the preferred orientation of quercetin within the NUDT5 substrate-binding pocket. AutoDock Vina docking program was to be used according to a predefined protocol. The docking search space was centered on the experimentally characterized inhibitor-binding region. The functional dimer was considered during receptor preparation. The docking procedure was validated by removing the co-crystallized ligand and redocking it into the prepared receptor. The predicted pose was compared with the experimentally determined pose using the RMSD of corresponding heavy atoms. A redocking RMSD below approximately 2 Å was considered a commonly used indication of pose reproduction, although it does not independently establish the accuracy of predicted binding affinities. The resulting quercetin poses were ranked using the selected scoring function. The preferred pose was examined for hydrogen bonds, hydrophobic contacts, aromatic stacking, and other relevant non-covalent interactions. Particular attention was given to Trp28A, Arg51A, Trp46B, and Glu47B because these residues have been implicated in the recognition of NUDT5 inhibitors. The docking score was reported in the units specified by the software, typically kcal/mol for AutoDock Vina. It was interpreted as a computational ranking metric rather than an experimentally measured binding free energy.

Molecular dynamics simulation

Molecular dynamics simulations were to be performed using a validated simulation package, such as AMBER, or NAMD. The production simulation duration was selected to provide sufficient sampling of the protein–ligand complex. A 100-200 ns trajectory could serve as an initial investigation, subject to computational feasibility and evidence of adequate equilibration.

Following energy minimization, the system was equilibrated under constant-volume and constant-pressure conditions as appropriate. Temperature and pressure were controlled using documented algorithms, while long-range electrostatic interactions were treated using an appropriate method, such as particle-mesh Ewald. The production trajectory was generated using a suitable integration time step and saved at intervals sufficient for subsequent structural and energetic analyses. The stability of the system was examined during equilibration before the production trajectory was accepted for analysis.

Results and Discussion

Molecular docking analysis was performed to investigate the binding potential of quercetin within the substrate-binding pocket of NUDT5. As presented in Table 1, nine docking poses were generated, with binding affinity scores ranging from -8.15 to -9.19 kcal/mol. The first-ranked pose (Mode 1) exhibited the most favorable predicted binding affinity of -9.19 kcal/mol, with RMSD upper-bound (RMSD/ub) and lower-bound (RMSD/lb) values of 0 Å. The second-ranked pose showed a binding affinity of -8.87 kcal/mol, followed by Mode 3 at -8.82 kcal/mol and Mode 4 at -8.64 kcal/mol. The negative docking scores indicate favorable predicted interactions between quercetin and the NUDT5 binding pocket according to the docking scoring function. The relatively favorable scores across the generated poses suggest that

Table 1: Energy values describing the binding affinity of NUDT5-quercetin complex interaction

Mode	rmsd/ub	rmsd/lb	Binding Affinity (kcal/mol)
1	0	0	-9.19
2	6.107	4.206	-8.87
3	18.245	13.231	-8.82
4	28.234	24.324	-8.64
5	26.856	22.647	-8.42
6	14.234	13.254	-8.41
7	8.524	4.864	-8.27
8	32.456	28.457	-8.21
9	8.964	4.235	-8.15

quercetin may adopt multiple energetically favorable orientations within the predicted binding site. The best-ranked pose was therefore selected for further examination of its molecular interactions with key residues, including Trp28A, Arg51A, Trp46B, and Glu47B, which contribute to ligand recognition in the NUDT5 dimeric binding pocket. Overall, the docking results support the computational plausibility of quercetin binding to NUDT5. However, docking scores alone do not establish inhibitory activity or biological efficacy. Further analysis of residue-level interactions, molecular dynamics trajectories, and binding free-energy estimates, followed by experimental validation, is required to assess the stability and functional significance of the predicted NUDT5–quercetin complex. The biological rationale for investigating NUDT5 is supported by previous experimental research demonstrating its involvement in hormone-dependent signaling and cellular proliferation in breast cancer. Page et al. (2018) showed that targeted NUDT5 inhibitors can interfere with hormone-dependent gene regulation, providing a foundation for continued research into compounds that modulate this enzyme. The relevance of quercetin as a candidate phytochemical is supported by its occurrence in edible plants, including *C. album*. Arora and Itankar (2018) reported the isolation and structural characterization of quercetin from the aerial parts of this species. This evidence establishes a botanical context for the compound investigated here. However, the computational study does not establish that *C. album* extracts inhibit NUDT5 or that the biological activities of the plant are attributable to quercetin alone. The interpretation of docking results requires particular caution. A favorable docking score indicates that a predicted pose is ranked favorably according to the selected scoring function. It does not establish a measured dissociation constant, catalytic inhibition, or target selectivity. The accuracy of the prediction depends on receptor preparation, ligand protonation, conformational sampling, treatment of solvent, and the scoring method. Docking validation through redocking the co-crystallized ligand can provide evidence that the selected protocol reproduces a known binding orientation. However, successful redocking does not guarantee accurate ranking of chemically different ligands. The docking score should therefore be interpreted alongside the observed interaction pattern and the subsequent dynamic analysis.

Molecular dynamics simulation can provide additional information about the persistence of a predicted binding pose (Zhao & Caflisch, 2015). RMSD describes conformational deviation, while RMSF characterizes local residue flexibility. Radius of gyration and SASA provide complementary information about protein compactness and solvent exposure. Hydrogen-bond occupancy can help identify persistent polar interactions, although hydrogen bonding is only one component of protein–ligand recognition (Raschka et al., 2018). The results should be interpreted according to the actual trajectory behavior. If the ligand RMSD stabilizes and key interactions persist, these findings may support the structural plausibility of the modeled complex under the simulation conditions. Conversely, substantial fluctuations, rearrangement of the ligand pose, or loss of initial interactions should be reported transparently. Neither a stable RMSD nor a persistent hydrogen bond alone proves high affinity or biological activity (Pavan et al., 2022). Binding free-energy estimation may provide complementary evidence concerning the modeled interaction. MM/GBSA and MM/PBSA methods incorporate molecular mechanics and approximate solvation contributions, but their estimates depend on sampling, parameterization, and methodological assumptions. Comparisons are most informative when performed using consistent protocols and suitable reference compounds (Xu et al., 2025).

An important consideration is the existing literature. Gligorić et al. (2025) have already investigated quercetin and its structural analogues against NUDT5 through molecular docking, MM/GBSA calculations, and pharmacokinetic predictions. Consequently, the present work must establish its contribution through the quality and reproducibility of the MD analysis, a critical comparison with published findings, and additional information about the persistence of quercetin-NUDT5 interactions.

The botanical origin of quercetin provides useful context but, by itself, does not establish computational novelty. If the present analysis identifies a stable and energetically favorable complex, the results may justify further investigation of quercetin as a candidate NUDT5-binding molecule. Nevertheless, the biological relevance of the interaction remains uncertain until direct biochemical experiments are conducted. The next stage should include an enzyme-activity assay to determine whether quercetin inhibits NUDT5 in a concentration-dependent manner. Appropriate controls should include a validated NUDT5 inhibitor, such as TH5427, where suitable for the assay. Additional experiments should investigate target engagement, selectivity, and cellular effects in relevant breast cancer models. Cell viability alone would not establish that an observed effect is mediated by NUDT5.

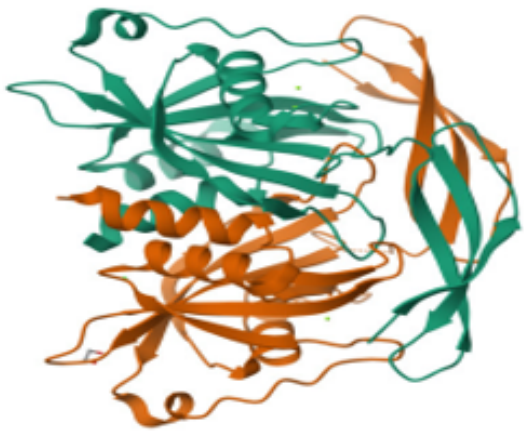


Fig. 1: 3D Structure of NUDT5

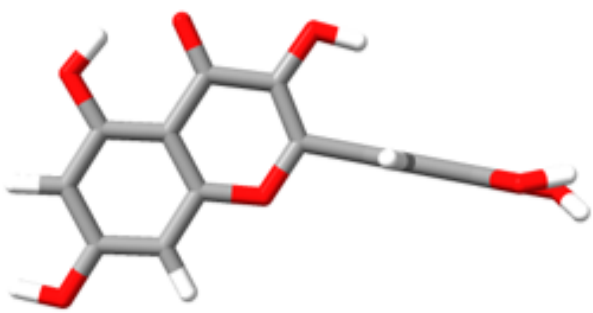


Fig. 2: 3D Structure of quercetin

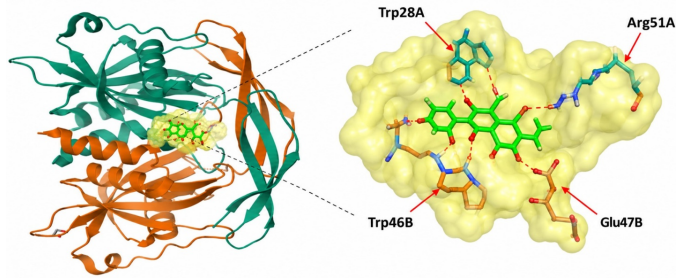


Fig. 3: Structural and functional core of the NUDT5-ligand complex

Conclusion

This study used molecular docking to examine the predicted interaction between quercetin, a flavonoid reported in Chenopodium album L., and Nudix hydrolase 5 (NUDT5). Quercetin showed favorable predicted binding, with the top-ranked pose scoring -9.19 kcal/mol, suggesting it can be accommodated within the NUDT5 binding pocket. Given the reported involvement of NUDT5 in hormone-dependent signaling and breast cancer cell proliferation, this finding offers a preliminary rationale for exploring quercetin in cancer research. However, docking scores are predictive estimates, and the approach has inherent limitations, including the use of a rigid receptor and the absence of explicit solvent effects, so the results do not establish NUDT5 inhibition or anticancer activity. Molecular dynamics simulations, binding free-energy calculations, enzyme-inhibition assays, and cell-based studies are needed to evaluate complex stability, target engagement, and biological efficacy. The quercetin content of C. album extracts should also be quantified experimentally before any pharmacological effects are attributed to the plant. Overall, these findings provide a computational starting point for further investigation of the quercetin-NUDT5 interaction.

Conflicts of interest and financial disclosures

The authors state that there are no conflicts of interest to disclose.

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