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Original Article

Mechanistic Investigation of Hidden Flavonoids Isoorientin and Hyperin as Pancreatic Lipase Inhibitors Using Molecular Simulations and Machine Learning Correlation

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ABSTRACT

Background: Phytochemicals exhibit diverse therapeutic properties with minimal adverse effects and documented their benefits against metabolic disorders. Inhibition of pancreatic lipase is a validated strategy for managing obesity and metabolic syndrome. **Objectives:** To statistically analyze experimentally reported pancreatic lipase inhibitory activities of selected phytoconstituents and to evaluate the binding affinity and stability of isoorientin and hyperin using molecular docking and Molecular Dynamics (MD) simulations. **Materials and Methods:** Using machine learning based tools such as correlation analysis and frequency distribution phytocompounds were ranked by occurrence frequency, and uncharted flavonoids Isoorientin and Hyperin were selected for *in silico* evaluation. Molecular docking was performed using Glide XP against Pancreatic Lipase (PDB: 1LPB). MD Simulations (100 ns) were conducted using the Desmond package with the OPLS force field and TIP4P water model. Structural stability was assessed using RMSD, RMSF, and interaction profiling. **Results:** Isoorientin showed a low median IC_{50} with narrow variability, indicating strong and reproducible inhibition, while hyperin demonstrated consistent moderate potency. Docking studies revealed favorable binding affinities of both the compounds with extensive hydrogen bonding, hydrophobic, and π-π interactions within the catalytic site, surpassing orlistat in docking scores. MD simulations confirmed stable complex formation with minimal conformational fluctuations and persistent intermolecular interactions. **Conclusion:** Isoorientin and hyperin exhibit reliable pancreatic lipase inhibitory potential, supported by statistical and computational analyses, highlighting their promise as lead candidates for metabolic disorder management.

Keywords: Binding affinity, Molecular docking, Molecular dynamics, Orlistat.

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INTRODUCTION

Obesity is a pervasive metabolic disorder that significantly heightens the risk of type 2 diabetes, cardiovascular diseases, and other chronic conditions, representing a pressing global health challenge with rapidly rising prevalence (Ahmed *et al*., 2025). Recent research highlights that, beyond lifestyle interventions, plant-derived phytoconstituents are emerging as promising, multi-targeted agents in obesity management (Ofoezie *et al*., 2025). These bioactive compounds-such as catechins, hydroxycitric acid, resveratrol, naringenin, β-sitosterol, and curcumin-have demonstrated potential to modulate key mechanisms including appetite suppression, lipid metabolism, energy expenditure, adipogenesis, and chronic inflammation in preclinical and clinical studies, often with fewer side effects compared to conventional drugs (Thapa *et al*., 2026).

Contemporary scientific investigations have substantiated an extensive repertoire of therapeutic benefits emanating from the judicious utilization of phytochemicals, particularly their remarkable efficacy in ameliorating multifaceted metabolic perturbations. The inherent bioactive properties of numerous phytochemical constituents confer distinctive advantages that render them exceptionally compelling for therapeutic applications, predominantly attributable to their negligible adverse effect profiles and their intrinsic integration within the human dietary matrix, even when administered at therapeutically efficacious concentrations (Hossain *et al*., 2025). Accumulating evidence substantiates the hypothesis that phytochemicals can orchestrate synergistic interactions, thereby augmenting the therapeutic efficacy of conventional pharmacological interventions targeting metabolic pathologies (Darko *et al*., 2025). Consequently, phytochemical compounds indigenous to diverse alimentary

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sources and beverages undergo systematic evaluation to elucidate their potential in attenuating metabolic disease-associated complications. Among these bioactive entities, flavonoids have consistently demonstrated substantial prophylactic potential against metabolic syndrome through diverse mechanistic pathways (Chen *et al*., 2025).

Isoorientin**,** a naturally occurring C-glucosyl flavone, has garnered considerable scientific attention owing to its diverse pharmacological repertoire (Figure 1a). Burgeoning experimental evidence corroborates the pivotal role of isoorientin's robust antioxidative and anti-inflammatory properties in mitigating numerous metabolic complications (Anilkumar *et al*., 2017). Botanical specimens enriched with isoorientin have exhibited pronounced ameliorative effects against metabolic aberrations, including hyperglycemia, dyslipidemia, and insulin resistance syndrome (Chua *et al*., 2020).

Hyperin (quercetin-3-O-galactoside (Figure 1b)), alternatively designated as hyperoside, represents a flavonol glycoside constituent ubiquitously distributed across diverse botanical species, including *Hypericum perforatum* L., *Alpinia officinarum, Silybum marianum*, and *Crataegus pinnatifida*, in addition to numerous vegetables and fruits (Hua *et al*., 2023). Previous literature attributes multifarious biological activities to hyperin, encompassing anti-apoptotic, anti-inflammatory, antidepressant, and anti-hyperglycemic properties (Wu *et al*., 2020).

The convergence of molecular docking, Molecular Dynamics (MD) simulations, and Machine Learning (ML) methodologies facilitates expeditious *in silico* screening and comprehensive evaluation of phytoconstituents for pharmaceutical discovery applications (Pandey *et al*., 2025). Machine learning algorithms enable the identification of potential lead compounds from extensive molecular databases, while molecular docking investigations provide quantitative assessments of binding affinities and optimal ligand-target orientations (Kuttappan *et al*., 2024). Subsequently, MD simulations validate these computational predictions through rigorous stability analyses, incorporating Root Mean Square Deviation (RMSD), Root Mean Square Fluctuation (RMSF), and Solvent-Accessible Surface Area (SASA) evaluations across temporal dimensions.

Accordingly, the present investigation aims to integrate machine learning-aided correlation and frequency distribution analyses with molecular docking and molecular dynamics simulations to systematically evaluate the pancreatic lipase inhibitory potential of two selected flavonoids, Isoorientin and Hyperin. By correlating experimentally reported inhibitory data with computational binding profiles and dynamic stability assessments, this study seeks to elucidate their structure-activity relationships and substantiate their therapeutic relevance in metabolic disorder management.

MATERIALS AND METHODS

Correlation and Frequency Distribution Analysis of Phytoconstituents

The present study was designed as an extension of our previously published research article (Sowmya *et al*., 2025), in which predictive modeling approaches were employed to identify potential phytochemical inhibitors of Pancreatic lipase. In contrast to the computational prediction framework reported earlier, the current investigation focuses on systematic statistical evaluation and frequency-based characterization of experimentally reported inhibitory data. IC_{50} values for selected phytoconstituents were comprehensively compiled from peer-reviewed experimental studies. Where available, multiple IC_{50} values per compound were recorded to capture inter-study variability. All values were standardized to uniform concentration units (μM) prior to analysis to ensure data consistency and comparability across independent reports.

Compounds were ranked in descending order of frequency, and the top 20 most frequently reported phytochemicals were selected for visualization to illustrate distribution patterns. Parallel frequency assessments were conducted for key experimental parameters, including solvent systems, substrate specificity, and study design variations. Statistical correlation analysis was subsequently applied using Pearson's correlation coefficient (r) to quantify linear relationships among IC_{50} values, compound-related variables, and experimental conditions (Koul *et al*., 2023).

Furthermore, IC_{50} values were stratified according to categorical variables-compound identity, solvent medium, and substrate specificity-to enable systematic potency comparison. Mean IC_{50} values were calculated for each category, and phytoconstituents exhibiting lower mean IC_{50} values were designated as more potent inhibitors, in accordance with established pharmacological principles. Solvent-specific comparative analyses were also conducted to determine the most efficacious compounds under distinct assay conditions.

Molecular Docking Studies

Molecular docking investigations were conducted using Glide 5.5 XP (Maestro Schrödinger suite 2022-4, Linux 64) to systematically evaluate the binding interactions of Isoorientin and Hyperin with the pancreatic lipase-colipase complex (PDB: 1LPB, resolution: 2.46 Å).

Protein Preparation

Crystal structures were retrieved from the Protein Data Bank and subjected to comprehensive preparation protocols. Extraneous chains and water molecules located beyond 5 Å from co-crystallized ligands were systematically removed. Subsequently, energy minimization was performed to generate

optimized crystal structures suitable for docking calculations. Receptor grids were strategically centered on the catalytic triad region of the lipase-colipase complex and the active site of the human fatty acid synthase thioesterase domain (Liu *et al.*, 2010).

Ligand Preparation

The three-dimensional molecular structures of Isoorientin, Hyperin and Orlistat were prepared using LigPrep with the OPLS 2005 force field. This preparation protocol encompassed the generation of multiple tautomeric forms and ionization states corresponding to physiological pH conditions (pH 7.4), ensuring comprehensive conformational sampling of both flavonoid compounds (Auti *et al.*, 2025).

Docking Protocol

Molecular docking simulations were performed using the Extra Precision (XP) mode of Glide to ensure comprehensive sampling of ligand conformations for Isoorientin and Hyperin. The prepared ligands were docked into the predefined active site of the target protein, and multiple binding poses were generated for each compound. These poses were ranked according to the XP scoring function, which integrates several interaction parameters, including hydrogen bonding with critical active site residues, hydrophobic contacts within the binding pocket, π-π stacking interactions with aromatic amino acid residues, and electrostatic complementarity between the ligands and receptor surfaces. The optimal binding conformations were selected based on their binding affinities, expressed as Glide scores (kcal/mol), along with detailed evaluation of hydrogen bond formation with key catalytic residues, π-π stacking interactions with aromatic amino acids, and overall spatial complementarity within the active site (Okoroechi *et al.*, 2023).

Molecular Dynamics Simulations

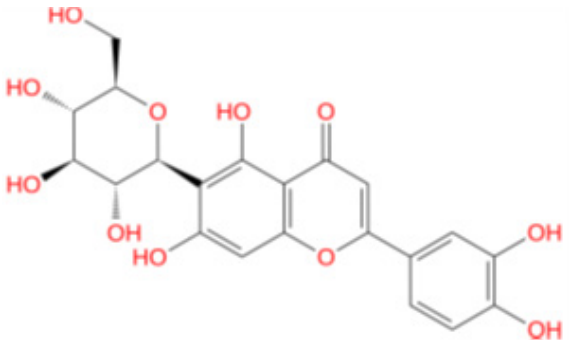
The dynamic behavior and binding stability of Pancreatic lipase (PDB ID: 1LPB) in complex with Isoorientin and Hyperin were investigated through extensive Molecular Dynamics (MD) simulations using the Desmond simulation package. System parameterization was performed employing the OPLS force field, and solvation was carried out using the TIP4P explicit water model. Each protein-ligand complex (pancreatic lipase-Isoorientin and pancreatic lipase-Hyperin) was embedded in an orthorhombic simulation box with a 10 Å buffer distance between the protein surface and the box boundaries to ensure adequate solvation. Overlapping solvent molecules were removed, and Na^+ counterions were added to neutralize the overall system charge (Nagarjuna *et al.*, 2025).

Prior to the production phase, energy minimization and equilibration were conducted under OPLS force field parameters to stabilize the systems. Production MD simulations were performed at a constant temperature of 300 K with an integration time step of 2.0 fs, and trajectories were recorded as 1000 frames at 20 ps intervals. The conformational stability of both complexes was evaluated by monitoring Root Mean Square Deviation (RMSD) values throughout the simulation. Post-simulation analyses included detailed assessment of structural interaction patterns, binding site occupancy, intermolecular contact frequencies, and dynamic fluctuations in binding modes (Zhao *et al.*, 2025).

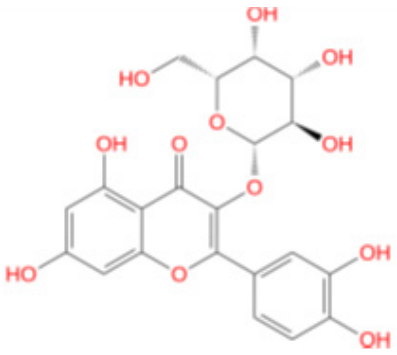
RESULTS

Correlation and Frequency distribution analysis

In our previous studies Isoorientin and Hyperin ranked among the commonly investigated phytoconstituents, highlighting sustained research interest. Distribution profiling showed that Isoorientin exhibited a low median IC_{50}, indicating strong and reproducible inhibition, while Hyperin maintained a stable median with moderate dispersion, reflecting consistent activity. In contrast, several other compounds displayed higher median IC_{50} values or wider variability (Figure 2). Overall, these findings support the reliable inhibitory potential of Isoorientin and Hyperin and justify their prioritization for further pharmacological evaluation.

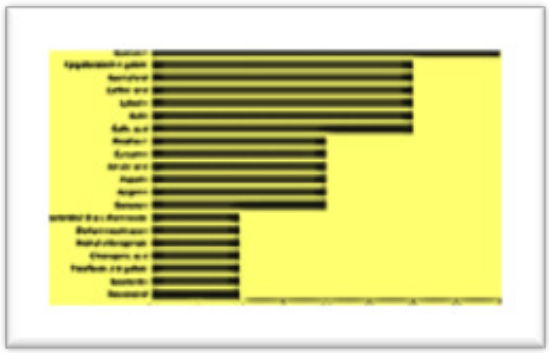


1a. Isoorientin

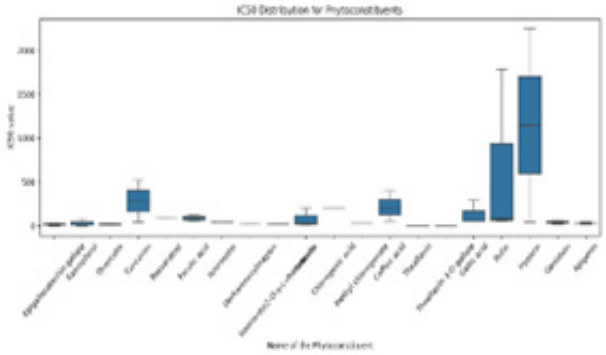


1b. Hyperin

Figure 1: Chemical structures of Isoorientin and Hyperin.



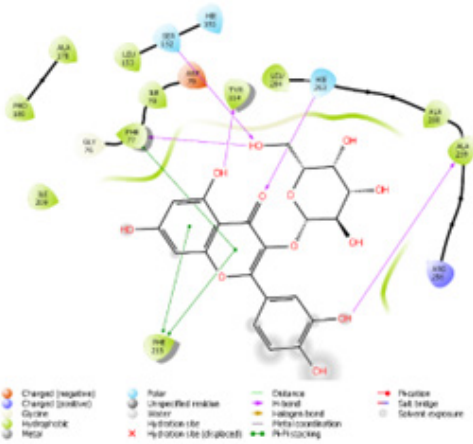
2a. Most frequent top 20 Phytoconstituents



2b. IC_{50} distribution of top 20 Phytoconstituents

Figure 2: Top 20 Most frequent phytoconstituents with their IC_{50} distribution.

3a. 2D interactions of Isorinentin with 1LPB



3b. 2D interactions of Hyperin with 1LPB

Figure 3: Molecular docking - 2D interactions of Isoorientin and Hyperin with 1LPB.

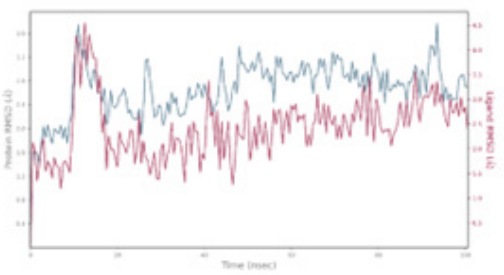
Molecular docking studies

Isoorientin and Hyperin showed significant binding affinities for pancreatic lipase (1LPB) highlighting their potential as modulators of important enzyme involved in lipid metabolism reflecting favorable ligand-protein complementarity and optimal positioning within the active site. Detailed inspection of the binding poses showed that both Isoorientin and Hyperin formed multiple stabilizing interactions, including hydrogen bonds with catalytic residues, π-π stacking with aromatic amino acids, and hydrophobic contacts within the binding pocket. Compared to Orlistat, these two ligands displayed superior docking scores and more extensive interaction networks, suggesting enhanced affinity and specificity for pancreatic lipase. Collectively, these results highlight Isoorientin and Hyperin as promising candidates for further mechanistic studies and experimental validation in the context of lipid metabolism regulation (Table 1 and Figure 3).

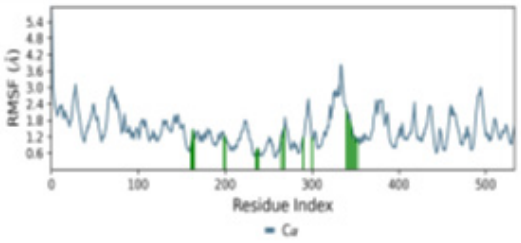
Molecular Dynamics

The molecular dynamics simulation of the pancreatic lipase-Isoorientin complex exhibited strong structural integrity over 100 ns. The RMSD profiles of both the protein and Isoorientin indicated consistent equilibration without significant deviations, confirming stable complex formation. RMSF results demonstrated reduced flexibility at the binding site residues, reflecting effective stabilization upon ligand binding. Isoorientin established stable hydrogen bonding networks along with hydrophobic and solvent-mediated interactions within the catalytic region, enhancing overall binding persistence. The ligand maintained conformational stability with minimal torsional fluctuations and sustained compactness throughout the simulation, as illustrated in Figure 4.

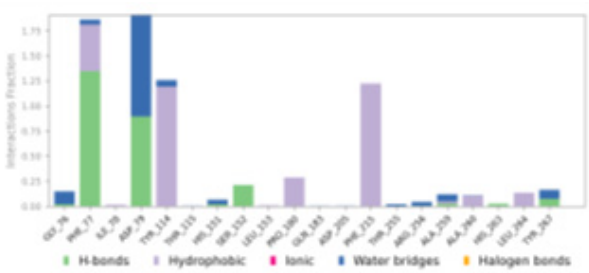
Similarly, the 100 ns molecular dynamics simulation of the pancreatic lipase-Hyperin complex (PDB ID: 1LPB) demonstrated high structural stability throughout the trajectory. The protein and ligand RMSD values remained well equilibrated, indicating that Hyperin maintained a stable binding orientation within the active site. RMSF analysis revealed minimal residue fluctuations, particularly at the catalytic pocket, suggesting ligand-induced stabilization of key functional regions. Hyperin formed persistent hydrogen bonds, hydrophobic interactions, and water-mediated contacts with important catalytic residues, contributing to sustained interaction stability. Additionally, the ligand showed



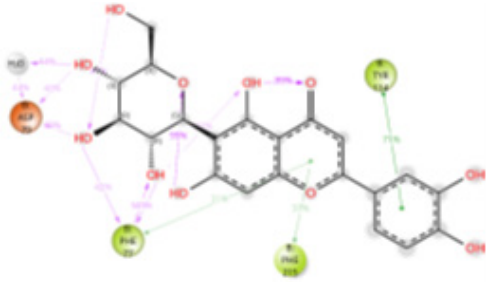
4a. RMSD of Protein ligand RMSD of Isoorientin



4b. Protein RMSF



4c. Protein Ligand contacts



4d. Ligand Protein contacts

Figure 4: Molecular dynamic simulations of Pancreatic lipase-Isoorientin complex.

Table 1: Molecular docking scores.

Name of the ligand	1LPB
Isoorientin	-11.7094
Hyperin	-10.008
Orlistat	-5.69255

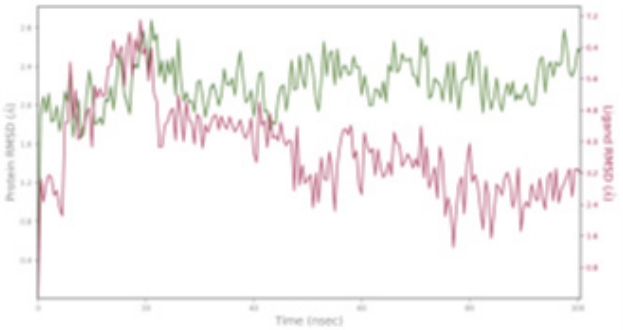
negligible conformational drift, preserving stable torsional angles and compact structural behavior over the simulation period (Figure 5).

DISCUSSION

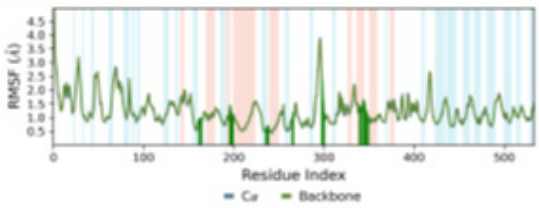
The global obesity crisis is closely linked to the metabolism of dietary fats, a process largely regulated by pancreatic lipase-an essential enzyme responsible for lipid hydrolysis into absorbable fatty acids (Subramaniyan *et al.*, 2025). Targeting pancreatic lipase has emerged as a promising therapeutic strategy for obesity management. Inhibiting this enzyme reduces intestinal fat absorption, lowers caloric intake, and supports weight control (Logesh *et al.*, 2020). Consequently, pancreatic lipase inhibition has become a key approach in the discovery of anti-obesity drugs. Recent research has increasingly focused on identifying natural inhibitors of pancreatic lipase that offer efficacy with minimal adverse effects (Citriniti *et al.*, 2025). In our previous study, a dataset compiled from approximately 55 research articles enabled the identification of several potent and frequently reported phytoconstituents with low IC_{50} values against pancreatic lipase. Among these, correlation and frequency distribution analysis placed isoorientin and hyperin among the top 20 compounds. Further, isoorientin and hyperin remain comparatively underexplored despite their promising inhibitory potential. Therefore, the present study specifically focuses on these two phytoconstituents to comprehensively evaluate their anti-obesity potential through *in silico* approaches.

Molecular docking outcomes of Isoorientin and hyperin, further substantiate prior computational studies reporting favorable binding affinities of polyphenolic compounds within the catalytic triad region of pancreatic lipase (Vidhya *et al.*, 2023). Similar to earlier reports highlighting hydrogen bonding, π-π stacking, and hydrophobic contacts as key stabilizing forces, Isoorientin and Hyperin demonstrated extensive interaction networks within the active site (Deogratias *et al.*, 2022). Notably, both compounds exhibited docking scores supporting their potential as competitive modulators of lipid metabolism.

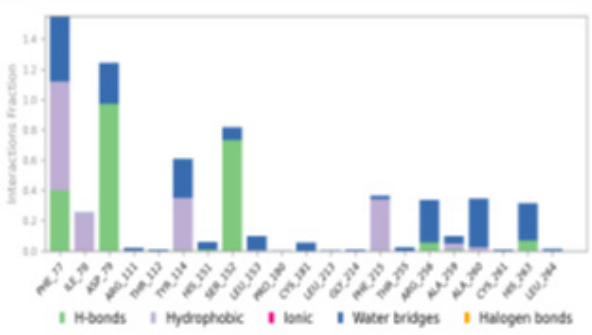
Consistent with earlier molecular dynamics investigations of flavonoid-enzyme complexes, the molecular dynamic simulations in this study demonstrated stable RMSD and RMSF profiles with persistent intermolecular contacts (Garg *et al.*, 2023). Collectively, these findings strengthen the validity of our integrative computational approach and further position Isoorientin and Hyperin as promising candidates for pancreatic lipase inhibition.



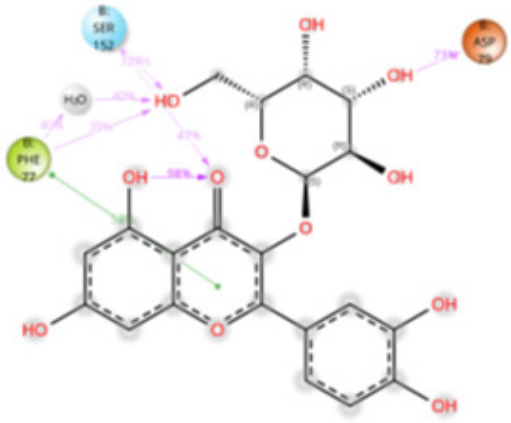
5a. RMSD of Protein ligand RMSD of Hyperin



5b. Protein RMSF



5c. Protein Ligand contacts



5d. Ligand Protein contacts

Figure 5: Molecular dynamic simulations of Pancreatic lipase-Hyperin complex.

CONCLUSION

Collectively, findings of present study establish a coherent structure-activity relationship framework and highlight Isoorientin and Hyperin as promising phytochemical candidates for further experimental validation and therapeutic development targeting metabolic disorders associated with dysregulated lipid metabolism.

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ABBREVIATIONS

IC_{50}: Half-maximal Inhibitory Concentration; **MD:** Molecular Dynamics; **ML:** Machine Learning; **PDB:** Protein Data Bank; **RMSD:** Root Mean Square Deviation; **RMSF:** Root Mean Square Fluctuation; **SASA:** Solvent-Accessible Surface Area; **XP:** Extra Precision; **OPLS:** Optimized Potentials for Liquid Simulations; **TIP4P:** Transferable Intermolecular Potential with 4 Points; **QSAR:** Quantitative Structure-Activity Relationship; **PM-USHA:** Pradhan Mantri Uchchatar Shiksha Abhiyan.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

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AUTHOR CONTRIBUTIONS

Sreedevi Adikay: Research concept and design, Critical revision of the article, Final approval of the article.

Sruthi Sai Kaveripakam: Research concept and design, Collection and/or assembly of data, Data analysis and interpretation, Writing the article, Final approval of the article.

Sowmya V Donthamsetty: Collection and/or assembly of data, Data analysis and interpretation.

Surekha Lakshmi Khandavilli: Collection and/or assembly of data, Writing the article.

SUMMARY

This study investigates the potential of two flavonoids, isoorientin and hyperin, as pancreatic lipase inhibitors for obesity management. Using a combination of machine learning correlation analysis, molecular docking, and molecular dynamics simulations, the research identifies these compounds as promising candidates. Results indicate that isoorientin and hyperin exhibit strong binding affinities and structural stability within the pancreatic lipase active site, comparable or superior to the standard drug orlistat. These findings support further experimental validation of these phytochemicals as therapeutic agents.

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