

STRUCTURE-BASED INVESTIGATION OF CURCUMIN–hIAPP FIBRIL INTERACTIONS THROUGH MOLECULAR DOCKING AND ADMET PROFILING

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ABSTRACT

Human islet amyloid polypeptide (hIAPP) aggregation and fibril formation is linked to pancreatic β -cell dysfunction in type 2 diabetes mellitus, and hIAPP could be a target molecule for anti-amyloid strategies. The molecular docking, binding interaction analysis and in silico absorption, distribution, metabolism, excretion and toxicity (ADMET) profiling of the interaction of curcumin with the hIAPP fibril were investigated in this study. The top nine docking poses predicted by AutoDock Vina have binding affinities ranging from -6.0 to -5.8 kcal/mol, and the most favorable docking pose has a binding affinity of -6.0 kcal/mol. The results from the interaction analysis showed that there is a multiresidue binding network around Ser20, Asn21, Asn22, Leu27, and Ser28 with conventional hydrogen bond, van der Waals contact and hydrophobic interaction. Curcumin showed moderate lipophilicity and suitable molecular size, but also low aqueous solubility, high plasma protein binding (PPB), low predicted BBB penetration, and high predicted BSEP, CYP1A2 and CYP2B6 inhibition. Comparatively low likelihoods for several endpoints were observed in toxicity predictions, whereas skin sensitization, respiratory toxicity, and hERG-related liability appeared as notable computational alerts. Overall, curcumin had a plausible predicted binding configuration with the hIAPP fibril and pharmacokinetic and safety limitations. These findings are the basis for further molecular dynamics, experimental fibrillation, pharmacokinetic and toxicity studies.

Keyword: Curcumin; hIAPP fibril; Molecular docking; Amyloid aggregation; ADMET

1. Introduction

In addition to insulin resistance and impaired glucose regulation, Type 2 Diabetes mellitus is accompanied by progressive β -cell failure and dysfunction. An increasing number of molecular characteristics that have been linked to such a loss are the aggregation of human islet amyloid polypeptide (hIAPP) or amylin, a polypeptide that is co-secreted with insulin by pancreatic β -cells. In the pathological condition, hIAPP can change its conformation and oligomerize and fibrilize, leading to oxidative stress, β -cell failure, cellular toxicity and membrane disruption (Bishoyi et al., 2021). This has made hIAPP an attractive molecular target for therapeutic approaches that seek to reduce amylin-induced damage to the pancreas in type 2 diabetes (T2D) (Roham et al., 2022).

The structure elucidation has significantly contributed to the knowledge of the organization of hIAPP fibrils and the molecular mechanisms that allow for their aggregation. Highly ordered fibrillar architectures and conserved amyloid cores were identified by cryo-electron microscopy and could define structurally defined binding sites for inhibitor interaction (Cao et al., 2020). Patient-derived fibrils have also revealed that hIAPP can exist in several polymorphic forms with the same core structure that is crucial for its biological function (Cao et al., 2021). Moreover, the structures of diabetes-associated variants of amylin have been compared, indicating that potentially surface-exposed regions may also play a role in the fibril assembly process, highlighting the importance of surface accessible regions in amyloid propagation (Gallardo et al., 2020). Recent studies also showed the importance of fibril-seeding mechanisms in the control of the structural progression of the hIAPP aggregation (Suladze et al., 2024).

Therapeutic approaches have focused on blocking aggregation of hIAPP or stabilizing non-toxic forms of it because aggregation may play a role in causing β -cell toxicity. Small peptides, molecules and natural compounds have been tested for their anti-fibrillating and anti-toxic effect (Tang et al., 2020). Peptides that inhibit aggregation of the hIAPP and block crucial stages in fibril formation are particularly promising candidates to target T2D segments of the hIAPP (Saini et al., 2020). Rationally designed peptides have also been shown to inhibit hIAPP fibrillation, with some studies suggesting these peptides can explain the mechanisms of aggregation (Rani et al., 2025). In summary, these results indicate that focusing directly on amyloidogenic regions could be a helpful approach in the development of anti-aggregation drugs.

In the small molecule screening, polyphenolic compounds have been found interesting for their ability to interact with amyloidogenic peptides via hydrogen-bonding, hydrophobic and aromatic interactions, as well as their structural diversity. Polyphenols have been extensively studied as hIAPP aggregation inhibitors in type 2 diabetes, where some compounds were identified as inhibitors of fibril formation and/or inhibitors of hIAPP aggregation-associated toxicity (Mahboob et al., 2023). In particular, curcumin, a natural polyphenol, is the compound that has been studied for its anti-inflammatory properties, its antioxidant activity and its ability to interact with the amyloid protein. It has been shown to be able to

interact with amyloid structure in various protein aggregation systems, suggesting that its potential relevance as an amyloid-binding scaffold (Radbakhsh et al., 2021). Additionally, molecular dynamics simulations have demonstrated that curcumin is able to interact with fibrillar structures and inhibit amyloid nucleation as well as create stabilizing interactions with fibrillar assemblies (Doytchinova et al., 2020; Jakubowski et al., 2020).

Evidence that links curcumin supplementation to decreased levels of islet amyloid polypeptide (IAPP) in people who have a high risk of metabolic and neurodegenerative disease provides further support for curcumin's possible role in hIAPP-related pathology (Thota et al., 2020). However, curcumin also has significant pharmacokinetic constraints, such as low water solubility, low systemic availability and inter-individual variability in oral bioavailability (Tabanelli et al., 2021). Such restrictions require the assessment of target binding activity, absorption, distribution, metabolism, excretion, and toxicity properties, and conclusions from this data as well as from the knowledge of its *in vivo* activity should be drawn regarding its drug development potential (Bučević Popović et al., 2024).

Computational methods offer a convenient platform for studying molecular recognition and pharmacokinetic properties. AutoDock Vina is a popular program for docking and scoring ligand–target complexes, as well as for estimating the binding strength of a ligand within a structurally defined binding region by identifying favorable interaction patterns (Eberhardt et al., 2021). At the same time, ADMET prediction platforms like ADMETlab 3.0 can be used in a systematic way for assessment of physicochemical, absorption, metabolic, transporter and toxicity properties in the early stages of compound assessment (Fu et al., 2024). Hence, the present study aimed to investigate the binding interaction of curcumin to hIAPP fibril by molecular docking and residue level interaction analysis and *in silico* ADMET profiling to analyze the physicochemical, pharmacokinetic, metabolic and toxicity property.

2. Materials and Methods

2.1 Study Design and Computational Workflow

In silico computational method was used to study the binding between hIAPP fibril and curcumin, and to analyze the pharmacokinetic and toxicity profile of curcumin. The analysis was divided into three parts that matched with the reported results: molecular docking with AutoDock Vina, characterization of binding interactions of the selected docking pose and ADMET prediction of curcumin.

2.2 Molecular Docking of Curcumin with the hIAPP Fibril

The AutoDock Vina software was used for molecular docking against the hIAPP fibril (Eberhardt et al., 2021). The docking search space was defined using grid dimensions of $82 \times 126 \times 84$ points (npts), with the grid center positioned at $x = -1.077$, $y = -0.891$, and $z = 0.772$. An exhaustiveness value of 20 was

used to increase the extent of conformational sampling during the docking search. The defined receptor space was subsequently explored to identify energetically favorable binding orientations of curcumin, and AutoDock Vina generated alternative binding modes with corresponding predicted binding affinities and RMSD values.

Nine docking poses were generated during the docking run. The poses were ranked based on predicted binding affinities, and a more negative docking score indicates a more favorable predicted ligand–receptor interaction. The pose with the lowest binding energy was chosen to represent the binding configuration and used for further interaction analysis. The curcumin output structure was obtained after the docking run (Curcumin_out.pdbqt) and docking search/refinement procedure was finished.

2.3 Docking Pose Selection and Evaluation

The outputs of the AutoDock Vina binding affinity and RMSD were used for the evaluation of the docking configurations generated. RMSD lower-bound and upper-bound were used to represent conformational differences between the docking modes, and binding affinity was represented in kcal/mol. The first ranked pose was used as the reference structure, having RMSD values of 0.000 Å. After the docking, nine poses were generated and stored that will be used for comparison.

The most favourable binding affinity was used as the criterion to choose the best ranked configuration. This specific configuration was then used to investigate molecular interactions between curcumin and residues of hIAPP fibril.

2.4 Binding Interaction Analysis

Three-dimensional and two-dimensional interaction analysis were performed on the top-ranked curcumin–hIAPP docking complex. The three-dimensional representation was used for visualizing the position and orientation of curcumin in the fibrillar binding region, while the two-dimensional interaction map was used to characterize the individual contact between the ligand and the residues.

The generated interaction profile was categorized to identify interactions, such as conventional hydrogen bonds, van der Waals, π -donor hydrogen bonds, alkyl and π -alkyl interactions. Interaction characterization included the identity of the residues and the designation of the peptide chain to identify if multiple hIAPP chains were contacted when the peptide chain contacted the curcumin. The residues in the immediate vicinity of the ligand and involved in polar or hydrophobic contacts were given special consideration. The interaction analysis was then carried out to determine the main residues that stabilize the docked pose of Curcumin from the selected pose.

2.5 ADMET and Physicochemical Property Analysis

The ADMET profile of curcumin was evaluated using the ADMETlab 3.0 output (Fu et al., 2024). Only physicochemical, drug-likeness, absorption, distribution, transporter, metabolism, excretion, and toxicity

parameters presented in the Results were considered for the analysis. Physicochemical and drug-likeness parameters were evaluated, such as molecular weight, topological polar surface area (TPSA), hydrogen-bond acceptors, rotatable bonds, number of rings, and other parameters (logP, logD, logS, quantitative estimate of drug-likeness (QED), Fsp³, and the Lipinski flag). These parameters were used to describe the molecular properties and for the prediction of drug likeness of curcumin.

2.6 Absorption, Distribution, Transporter, and Excretion Assessment

Caco-2 permeability, MDCK permeability, human intestinal absorption (HIA) and the F20, F30, and F50 endpoints were used to assess the absorption profile. Plasma protein binding (PPB), steady-state volume of distribution (VD_{ss}), fraction unbound in plasma (Fu), blood–brain barrier (BBB) penetration and PAMPA permeability were included in the distribution assessment. The predicted transporters were P-glycoprotein inhibitor, P-glycoprotein substrate, breast cancer resistance protein (BCRP) inhibitor, and bile salt export pump (BSEP) inhibitor. Elimination related parameters, such as half-life and plasma clearance, were evaluated and predicted. The endpoints for which the probability was calculated were kept in their predicted probability form and compared across ADMET characteristics.

2.7 Cytochrome P450 and Metabolic Assessment

The possible metabolism of curcumin was evaluated by the prediction of the interaction with the most important cytochrome P450 (CYP450) isoenzymes. The inhibition endpoints evaluated included CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6 and CYP3A4. The human liver microsomal endpoint was also added to the metabolic assessment. The CYP450 isoenzymes were compared in terms of their predicted probabilities to define the differences in the metabolic interaction profile of curcumin. To distinguish predictions above and below the classification threshold, a probability threshold of 0.5 was used.

2.8 Toxicity Assessment

Safety profile prediction of curcumin was done based on the toxicity end points provided in the ADMET output. The endpoints assessed included Ames mutagenicity, carcinogenicity, drug-induced liver injury (DILI), genotoxicity, human hepatotoxicity, hERG at 10 µM, general hERG liability, nephrotoxicity, neurotoxicity, ototoxicity, respiratory toxicity and skin sensitization. The predicted probability of each endpoint was used for each endpoint. Probability values were compared between endpoints to find relatively high and low predicted toxicity signals. A 0.5 probability threshold was used for a visual comparison of the predicted endpoints.

2.9 Ethical Considerations

This study was entirely computational, and human subjects, identifiable personal information, clinical manipulation, or experimental animals were not used. Only molecular docking, ligand–fibril interaction

characterization and in silico ADMET predictions were considered for the analyses. It is, therefore, concluded that no direct human or animal experiments were done for the present study.

3. Results

3.1 Molecular Docking of Curcumin with the hIAPP Fibril

The binding properties of curcumin to the human islet amyloid polypeptide (hIAPP) fibril were predicted by molecular docking. The number of possible binding modes generated by AutoDock Vina was 9 and the binding affinity was predicted between -6.0 to -5.8 kcal/mol. The top-ranked pose showed the best binding affinity of -6.0 kcal/mol and was chosen for further interaction analysis with the residues. The other poses had docking scores that were close together; modes 2–5 had docking affinities of -5.9 kcal/mol while modes 6–9 had docking affinities of -5.8 kcal/mol.

The first docking mode was found to be the reference conformation with RMSD lower and upper limits of 0.000 Å as presented in Table 1. The alternative poses, however, showed much higher ranges for the RMSD, from 15.470 to 40.841 Å for the lower bound and 17.836 to 41.773 Å for the upper bound. The results show that the calculated binding energies were comparable, but curcumin bound with different spatial orientations to the modeled fibrillar surface.

Table 1. AutoDock Vina docking results for curcumin against the hIAPP fibril

Docking pose	Binding affinity (kcal/mol)	RMSD lower bound (Å)	RMSD upper bound (Å)
Pose 1	-6.0	0.000	0.000
Pose 2	-5.9	40.559	41.773
Pose 3	-5.9	40.841	41.501
Pose 4	-5.9	16.616	18.871
Pose 5	-5.9	15.948	18.471
Pose 6	-5.8	17.901	19.897
Pose 7	-5.8	15.470	17.836
Pose 8	-5.8	15.754	18.003
Pose 9	-5.8	16.647	20.469

Figure 1 shows that the distribution of docking scores and the three-dimensional position of the top-ranking pose are displayed. The relatively short docking-energy interval suggests that multiple

energetically similar docking solutions were created, and the large RMSD differences suggest conformational heterogeneity within the docking solutions.

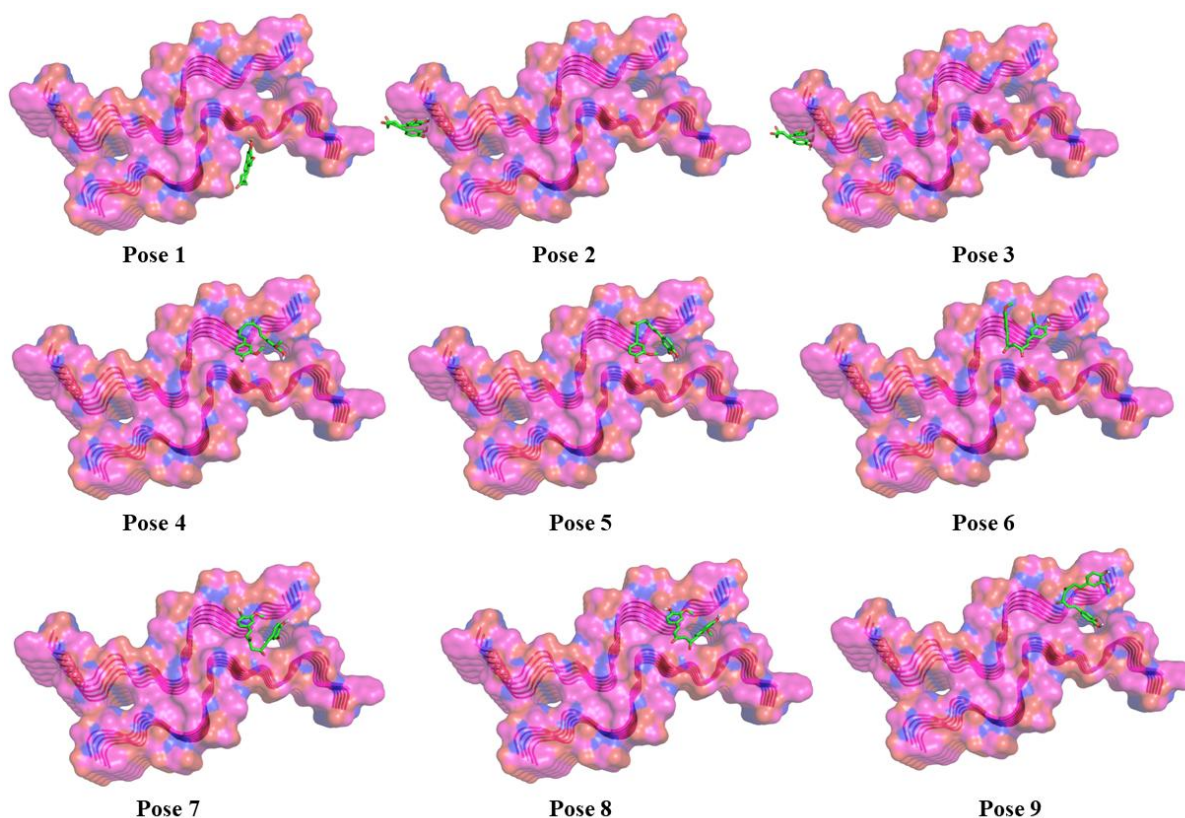


Figure 1. AutoDock Vina molecular docking of curcumin with the hIAPP fibril showing the ranked docking poses and the best-binding configuration.

3.2 Binding Interaction Profile of Curcumin with the hIAPP Fibril

The top-ranked docking pose of curcumin was further analyzed for interactions with details, and it was found that curcumin was embedded in a fibrillar binding region which is largely occupied by the residues of Ser20, Asn21, Asn22, Leu27, and Ser28, located in various chains of the hIAPP peptide. As seen in Figure 2, curcumin created a mixture of traditional hydrogen bonding, van der Waals contacts, π -donor hydrogen bonding and hydrophobic interactions between the alkyl group and the π -electrons.

The main features of the predicted binding network included hydrogen bonding. The functional groups that contain oxygen atoms, such as hydroxyl and carbonyl, were shown to repeatedly form conventional hydrogen-bond contacts with Ser20, Asn22, and Ser28. The interactions were spread out between different peptide chains, and the ligand appeared to bind to more than one chain of a fibrillar strand at a time. The phenolic OH and carbonyl groups of curcumin seem to make a significant contribution to these polar contacts.

Leu27 was mostly identified as a hydrophobic stabilizing residue involved in both alkyl and π -alkyl interactions with the aromatic and conjugated parts of curcumin. The additional van der Waals interactions between Asn21, Asn22, Ser20, and Leu27 all helped to accommodate the ligand. The two-dimensional interaction map also showed a π -donor hydrogen bond with the Asn22. The principal residue-level interactions are summarized in Table 2.

Table 2. Principal predicted interactions between curcumin and the hIAPP fibril

Interaction type	Principal hIAPP residue(s)	Chain(s) observed	Functional significance in the docking pose
Conventional hydrogen bond	Ser20	C, F	Polar stabilization involving curcumin oxygen groups
Conventional hydrogen bond	Asn22	C, F	Additional stabilization of the bound ligand
van der Waals	Asn21	B, C	Surface accommodation around curcumin
van der Waals	Asn22	B, J	Stabilization around central/terminal ligand regions
van der Waals	Ser20	B	Additional polar-contact environment
Conventional hydrogen bond	Ser28	B, F	Hydrogen-bond stabilization involving curcumin oxygen groups
Alkyl/ π -alkyl	Leu27	B, C, F, J	Hydrophobic interaction with curcumin aromatic/conjugated system
π -donor hydrogen bond	Asn22	B	Additional aromatic-polar interaction

Overall, the interaction pattern suggests a multiresidue and multi-chain binding network stabilizing the top-ranked pose of curcumin rather than a single dominant interaction between amino-acids. These were especially well represented by the residues of Ser20, Asn22, and Leu27 that provided polar and hydrophobic contacts around the ligand. The two- and three-dimensional interaction configuration is displayed in Figure 2.

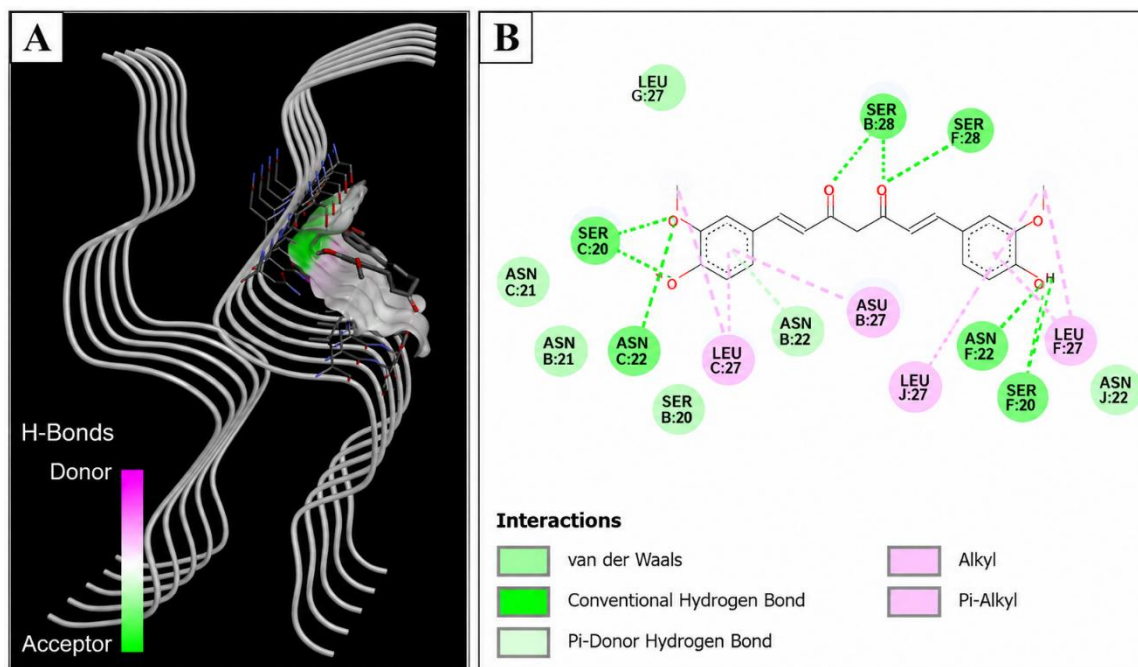


Figure 2. (A) Three-dimensional binding orientation and (B) two-dimensional interaction map of curcumin with the hIAPP fibril, showing the principal residue-level interactions.

3.3 Physicochemical Properties and Drug-Likeness of Curcumin

Table 3 shows the physicochemical and drug-likeness properties of curcumin. Curcumin has a molecular weight of 368.13 Da, topological polar surface area of 93.06 Å², six hydrogen-bond acceptors, two hydrogen-bond donors and eight rotatable bonds. Lipophilicity prediction values of logP and logD were 2.147 and 2.388, respectively, which was considered moderate.

The predicted aqueous solubility was relatively low (logS = -3.620). The quantitative estimate of drug-likeness (QED) was 0.548 indicating an intermediate drug-likeness profile. No Lipinski alert(s) were found in the provided ADMET output. All these parameters suggest that curcumin has generally acceptable conventional physicochemical properties, with water solubility being a possible limitation.

Table 3. Physicochemical and drug-likeness profile of curcumin

Parameter	Predicted value
Molecular weight	368.13 Da
TPSA	93.06 Å ²
Hydrogen-bond acceptors	6

Hydrogen-bond donors	2
Rotatable bonds	8
Number of rings	2
logP	2.147
logD	2.388
logS	-3.620
QED	0.548
Fsp ³	0.143
Lipinski flag	0

The overall physicochemical profile is graphically represented in Figure 3, which illustrates the balance between molecular size, lipophilicity, hydrogen-bonding capacity, polarity, and conformational flexibility.

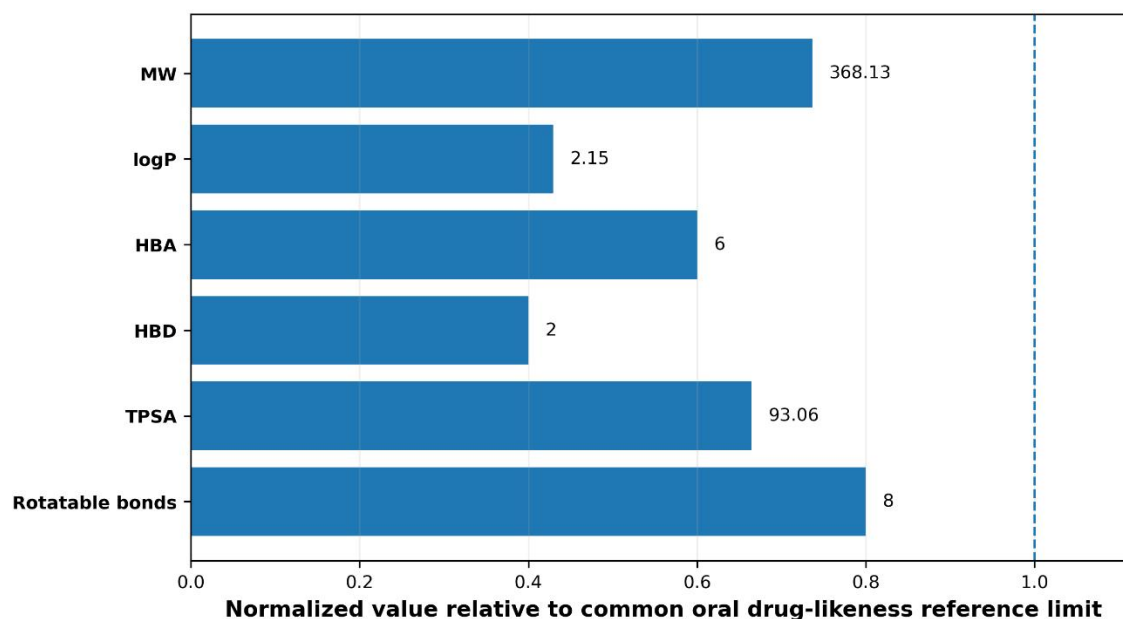


Figure 3. Physicochemical and drug-likeness profile of curcumin based on predicted molecular descriptors.

3.4 Absorption, Distribution, Metabolism, and Excretion Profile

Table 4 shows the predicted ADME properties of curcumin. The human intestinal absorption positive probability was relatively low (0.017) and the predicted probabilities for F20, F30 and F50 were 0.785,

0.479 and 0.999, respectively. The predicted Caco-2 permeability was -5.471 and MDCK permeability was 1.15×10^{-5} .

The plasma protein binding (PPB) was highly predicted (97.05%), and the volume of distribution at steady state (V_{ss}) was predicted to be 0.200 L/kg for curcumin. The blood-brain barrier penetration probability was low (0.023) and the probability for penetration positive in the PAMPA was also low (0.020).

Prediction by transporters indicated a low probability of P-glycoprotein substrate (0.009) and a high probability of P-glycoprotein inhibitor (0.280). One of the more salient transporter related alerts was BCRP inhibition, which was predicted to be 0.294, while BSEP inhibition was much larger at 0.937.

Table 4. Predicted ADME and transporter characteristics of curcumin

Parameter	Predicted value
Caco-2 permeability	-5.471
MDCK permeability	1.15×10^{-5}
HIA-positive probability	0.017
F20-positive probability	0.785
F30-positive probability	0.479
F50-positive probability	0.999
Plasma protein binding	97.05%
VD_{ss}	0.200 L/kg
BBB-positive probability	0.023
PAMPA-positive probability	0.020
P-gp inhibitor probability	0.280
P-gp substrate probability	0.009
BCRP inhibitor probability	0.294
BSEP inhibitor probability	0.937
Predicted half-life	1.040
Plasma clearance	8.522

As can be seen in Figure 4, there is significant inter-endpoint variability in the comparative absorption and distribution profile. A comparatively high probability was seen with F50, BSEP inhibition and F20, while a comparatively low probability was seen with BBB permeability, PAMPA permeability, HIA-positive status and P-gp substrate status.

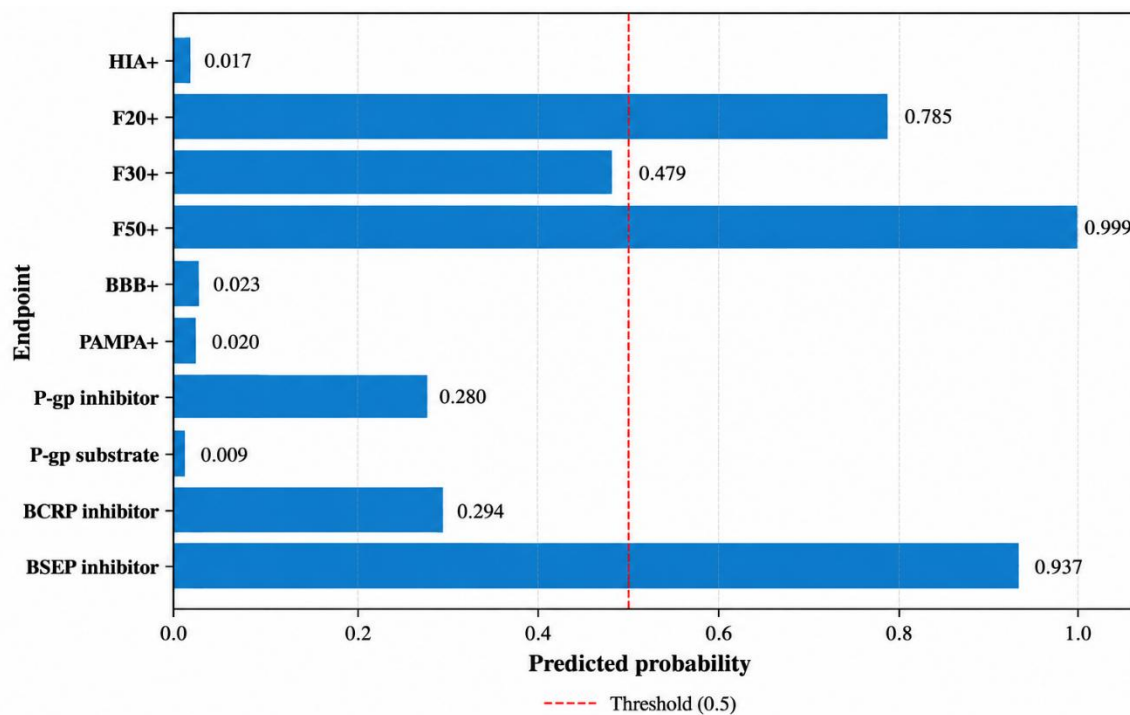


Figure 4. Predicted absorption, distribution, and transporter profile of curcumin.

3.5 Cytochrome P450 Metabolism Profile

As predicted in the metabolic profile, significant inter-isoenzyme variability was observed. The predicted probabilities of the inhibition of CYP1A2 and CYP2B6 were very high for curcumin as shown in Table 5. Compared with these, the CYP2C19 inhibition was intermediate at 0.491 while the CYP2C9 inhibition was lower at 0.269.

For the enzymes CYP2D6 and CYP3A4, very low inhibition probability was found (0.018 and 0.014 respectively). The human liver microsomal end point was predicted at 0.552, which is an intermediate metabolic-stability signal.

Table 5. Predicted CYP450 inhibition profile of curcumin

CYP450 isoenzyme	Inhibition probability
CYP1A2	0.996
CYP2B6	1.000

CYP2C19	0.491
CYP2C9	0.269
CYP2D6	0.018
CYP3A4	0.014
Human liver microsomal endpoint	0.552

CYP1A2 and CYP2B6 had the highest predicted inhibition probabilities among all the enzymes and were well separated from CYP2D6 and CYP3A4 (Figure 5). The results of this study indicate that CYP1A2 and CYP2B6 are the main metabolic liabilities of curcumin predicted during the analyzed ADMET profile.

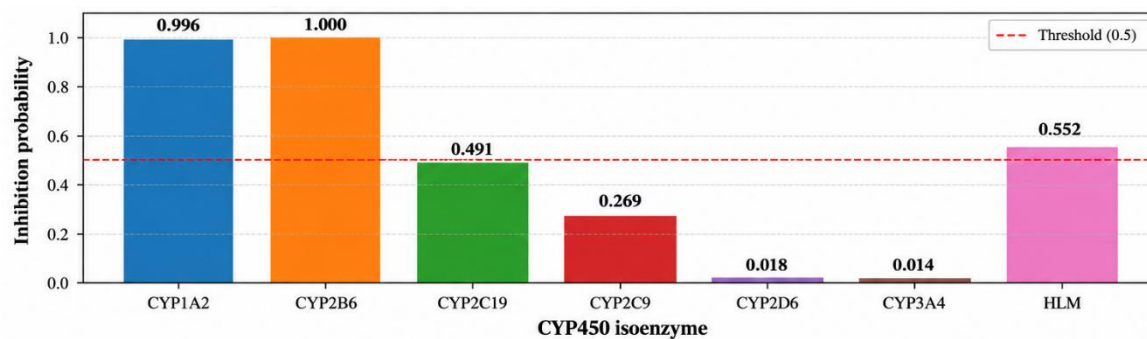


Figure 5. Predicted cytochrome P450 inhibition profile of curcumin.

3.6 Predicted Toxicity Profile

A summary of the predicted toxicological properties of curcumin is given in Table 6. The probabilities for several endpoints were relatively low, such as liver injury due to the drug (0.033), genotoxicity (0.043), ototoxicity (0.087), carcinogenicity (0.138) and nephrotoxicity (0.153). Ames mutagenicity was also less than 0.5 with a predicted probability of 0.293.

In contrast, increased prediction scores were found for selected safety endpoints. Skin sensitization was the most probable (0.995) and respiratory toxicity was the next most probable (0.762). The probability of the hERG 10- μ M endpoint was 0.634, while the wider hERG endpoint had a lower probability value of 0.437. The probabilities of human hepatotoxicity and neurotoxicity were intermediate, 0.429 and 0.418, respectively.

Table 6. Predicted toxicity profile of curcumin

Toxicity endpoint	Predicted probability
Ames mutagenicity	0.293

Carcinogenicity	0.138
Drug-induced liver injury	0.033
Genotoxicity	0.043
Human hepatotoxicity	0.429
hERG at 10 μ M	0.634
General hERG	0.437
Nephrotoxicity	0.153
Neurotoxicity	0.418
Ototoxicity	0.087
Respiratory toxicity	0.762
Skin sensitization	0.995

The comparative toxicity profile is shown in Figure 6. Skin sensitization showed the highest predicted toxicity probability followed by the respiratory toxicity and the hERG 10- μ M endpoint. By comparison, the model probabilities for drug-induced liver injury, genotoxicity and ototoxicity were comparatively low.

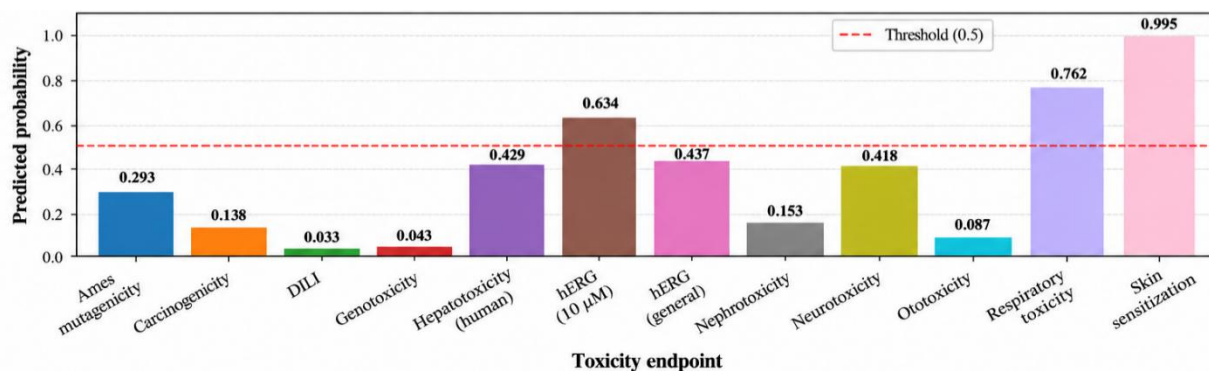


Figure 6. Comparative predicted toxicity profile of curcumin based on ADMET analysis.

4. Discussion

In the present study, the interaction of curcumin with the hIAPP fibril was molecularly docked, analyzed at the residue level and predicted using the ADMET method. The best binding affinity predicted by AutoDock Vina was of -6.0 kcal/mol and interaction map showed curcumin formed multiple interactions with residues Ser20, Asn21, Asn22, Leu27, and Ser28 of various hIAPP chains. These results support previous results and findings that the amyloidogenic region of hIAPP contains structurally accessible

binding sites for inhibitors as well as modulation of the organization of the fibrils (Cao et al., 2020; Suladze et al., 2024).

The importance of the involvement of Ser20, Asn22 and Leu27 is significant because residues in the central amyloidogenic region play a major role in the self-assembling and stability of hIAPP. Silybin-based inhibitory studies have also shown the ability to disrupt amyloid growth and toxicity by stereospecific interactions with the amyloidogenic region of the hIAPP (Garcia-Vinuales et al., 2022). This region has also been identified by computational studies of rationally designed peptides as important target to inhibit hIAPP aggregation (Kaur & Goyal, 2024). The interaction pattern supports predicted association of curcumin with a structurally important fibrillar region; however, molecular docking alone does not demonstrate inhibition of hIAPP fibrillation.

The complex of curcumin and hIAPP was stabilized by the conventional hydrogen bonding and van der Waals contacts as well as by hydrophobic alkyl/ π -alkyl interactions. It is known that polyphenolic molecules can bind to amyloid structures via both polar and aromatic interactions, making this multivalent binding possible (Mahboob et al., 2023). Likewise, molecular interactions such as aromatic and hydrogen bonding interactions are known to play a role in ligand recognition between curcumin and its derivatives with amyloid- β fibrils (Khurshid et al., 2022; Utomo et al., 2021). Additional molecular-dynamics studies have also suggested that curcumin may disrupt initial stages of amyloid nucleation and organization into fibrils (Doytchinova et al., 2020).

The same findings apply to amyloid biology in general. Oligomeric and fibrillar assemblies are known to be toxic in multiple protein-misfolding diseases, such as type 2 diabetes and neurodegenerative diseases (Nguyen et al., 2021). Mechanistic links between diabetic and neurodegenerative amyloid pathologies have also been shown through interactions between A β and IAPP (Al Adem et al., 2022). Thus, the therapeutic interest in hIAPP has grown, as it is involved in both metabolic dysfunction and amyloid-associated cellular toxicity (Alrouji et al., 2023; Li & Zhang, 2025).

This therapeutic paradigm has been broadened recently to include non-small molecule drugs. The development of hIAPP protofibril-specific antibodies has proved the potential of directly targeting pathogenic amyloid assemblies (Bortoletto et al., 2022). Computationally designed peptides derived from hIAPP have also demonstrated anti-fibrillation activity (Rani et al., 2026) that has been experimentally validated. The results support the importance of structure-guided methods, and confirm the need for experimental validation of structure-based inhibitors (Bousch et al., 2026).

The ADMET analysis showed mixed profile of curcumin for its developability. The molecular weight, the hydrogen-bonding capacity, TPSA and moderate lipophilicity were well suited to traditional drug-like properties, while the predicted logS of -3.620 suggested poor aqueous solubility. This is consistent with the formulation and bioavailability challenges of curcumin that is well established (Abd El-Hack et al., 2021; Tabanelli et al., 2021). Current pharmacologic evaluations also agree that inadequate absorption,

metabolism, and systemic bioavailability are still significant barriers to the translation of curcumin (Hao et al., 2023). There is also significant variability between different formulations and studies in systematic evaluations of the bioavailability of curcumin in the oral route (Bučević Popović et al., 2024).

The 97.05% plasma protein binding, low BBB probability and high BSEP-inhibition probability also suggest that while favourable docking does not always lead to favourable pharmacokinetics. In particular, CYP predictions indicated high probabilities of inhibition for CYP1A2 and CYP2B6, which could present a risk for metabolic interaction. Prediction platforms for ADMET are useful for predicting these early-stage liabilities, but their predictions are a computational estimate and would need to be confirmed experimentally (Fu et al., 2024; Jamrozik et al., 2024).

Compared to the others, the probability of DILI, genotoxicity, carcinogenicity, nephrotoxicity and ototoxicity were relatively low, while skin sensitization, respiratory toxicity, and hERG-related liability were more prominent alerts generated by toxicity prediction. Overall, these results suggest that curcumin has a potential predicted binding mode with the hIAPP fibril, while also having pharmacokinetic and safety issues. This interpretation aligns the general trends of the literature indicating curcumin as an amyloid interacting molecule but bearing in mind the limitations of its translational potential (Radbakhsh et al., 2021; Thota et al., 2020). In this light, the present findings further require experimental testing, molecular dynamics simulations, binding free-energy calculations, fibrillation assays, permeability assays and metabolic evaluation to confirm or refute anti-amyloid or therapeutic conclusions.

5. Conclusion

The present study used molecular docking, in silico ADMET profile and binding interaction analysis to investigate the interaction of curcumin with the hIAPP fibril. The best binding affinity from AutoDock Vina was -6.0 kcal/mol and the docked conformation showed a network of multiresidue interactions involving Ser20, Asn21, Asn22, Leu27 and Ser28. The interactions in the predicted complex were stabilized by conventional hydrogen bonding, van der Waals contacts, and hydrophobic alkyl/ π -alkyl interactions, and Ser20, Asn22, and Leu27 are highlighted residues for interactions.

The ADMET assessment revealed that the curcumin has generally acceptable drug-like and physico-chemical properties such as moderate lipophilicity and appropriate molecular size. However, there were also some limitations including low aqueous solubility, high plasma protein binding, low predicted BBB penetration and high probabilities of BSEP, CYP1A2 inhibition and CYP2B6 inhibition. Additional toxicity predictions identified skin sensitization, respiratory toxicity, and hERG liability as the top computational safety signals.

The results suggest a plausible predicted binding conformation for curcumin with the hIAPP fibril and also provide pharmacokinetic and safety properties that could be a constraint to its direct therapeutic use. In this light, the present findings would require further experimental testing, molecular dynamics

simulations, binding free-energy calculations, fibrillation assays, permeability assays and metabolic evaluation to confirm or refute anti-amyloid or therapeutic conclusions.

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