
Molecular Docking Of Bioactive Compounds From Mangosteen Peel (*Garcinia mangostana* L.) And Design Of New Quercetin Derivatives As MAO-A Inhibitors For Anti-Stress Potential

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Abstract

Stress is associated with an imbalance of neurotransmitters in the central nervous system. Monoamine Oxidase A (MAO-A) plays a role in the metabolism of monoamine neurotransmitters and therefore, has potential as a target for the development of anti-stress agents. Mangosteen peel (*Garcinia mangostana* L.) contains various bioactive compounds with potential for development as anti-stress agent candidates. This study aimed to analyze the interactions of bioactive compounds from mangosteen peel with MAO-A through molecular docking and to evaluate drug-likeness, ADME, toxicity, and structural modification of the selected compound. An in silico study was conducted on 70 bioactive compounds using PyRx-AutoDock Vina with MAO-A (PDB ID: 2Z5X). Validation was performed by redocking the native ligand Harmine. The selected compounds were subsequently analyzed using SwissADME, pkCSM, and Toxtree. Redocking of Harmine produced an RMSD of 1.581 Å and a binding affinity of -8.2 kcal/mol, indicating that the method was valid. The four best-performing compounds were Quercetin, Apigenin, Smeathxanthone A, and Epicatechin, with binding affinity of -9.0, -8.9, -8.6, and -7.4 kcal/mol, respectively. Quercetin was selected based on its lowest binding affinity and similarity of amino acid residue interactions with the native ligand. Modification of Quercetin produced (Z)-4-(prop-1-en-1-yl)-3,6-dihydro-[1,1'-biphenyl]-2,3',4'-triol with a binding affinity of -8.7 kcal/mol and an RMSD of 1.321 Å, accompanied by an improved ADME profile and low toxicity. The modified compound has potential for further development as an anti-stress agent candidate targeting MAO-A, however, further in vitro and in vivo studies are required.

Keywords: ADMET, Anti-Stress, *Garcinia mangostana* L., MAO-A, Molecular Docking

INTRODUCTION

Stress is a physiological and psychological response to pressure or demands perceived by an individual. Although stress is a part of daily life, high and persistent levels of stress can affect individual well-being and health (Chu *et al.*, 2021). This condition remains a global concern. According to the *State of the World's Emotional Health 2025*, 37% of adults worldwide reported experiencing a lot of stress on the previous day during 2024. The high prevalence of stress experiences indicates that emotional health remains an issue requiring global attention (Gallup, 2025).

Mental health problems are also a concern in Indonesia. Based on the Indonesian Health Survey (SKI) 2023, the prevalence of depression among the Indonesian population aged ≥15 years was 1.4%, while among those aged 15–24 years, it reached 2.0% (Kemenkes RI, 2024). According to the Indonesia-National Adolescent Mental Health Survey (I-NAMHS), 5.5% of adolescents aged 10–17 years experienced a mental disorder, and 34.9% experienced at least one mental health problem within the previous 12 months (I-NAMHS, 2022). These conditions highlight the importance of developing approaches that can support efforts to address mental health problems, particularly among younger populations.

Stress and mood disorders are associated with the monoamine neurotransmitter system, including serotonin, norepinephrine, and dopamine (Naai *et al.*, 2025). Monoamine Oxidase A (MAO-A) is an enzyme involved in the oxidative metabolism of monoamine neurotransmitters and is therefore, an important target in the development of agents for mood disorders. Monoamine oxidase inhibitors have been used in the treatment of depressive disorders; however, their use may be limited by adverse effects and potential interactions

with drugs and food. Therefore, the search for new compounds with MAO-A inhibitory potential and improved safety profiles remains necessary (Duarte *et al.*, 2021).

Natural products are potential sources for drug discovery and development because of their diverse chemical structures and biological activities (Wang *et al.*, 2024). Mangosteen (*Garcinia mangostana* L.) is a plant containing various bioactive compounds, particularly xanthenes, as well as phenolic compounds and flavonoids (Yan *et al.*, 2026). Various studies have reported that compounds from mangosteen possess biological activities, including antioxidant, anti-inflammatory, and neuroprotective activities. These activities indicate the potential of mangosteen bioactive compounds to support nervous system protection, although their specific therapeutic potential against particular targets requires further investigation (Zonouz *et al.*, 2023; Thew *et al.*, 2025).

In silico approaches can be used to support the discovery of natural product-based drug candidates. One widely used method is *molecular docking*, a computational method for predicting the orientation and interactions of ligands with target proteins and estimating their *binding affinity*. This method enables the preliminary screening of large numbers of compounds more efficiently before experimental testing (Atanasov *et al.*, 2021). Further evaluations of *drug-likeness*, ADME, and toxicity are also necessary to provide an initial assessment of the suitability of compounds as drug candidates.

The pharmacological potential of mangosteen peel has been widely reported. However, studies comprehensively screening various bioactive compounds from mangosteen peel as potential MAO-A inhibitors, followed by evaluations of *drug-likeness*, ADME, toxicity, and structural modification of selected compounds, remain limited. Therefore, this study was conducted to analyze the interactions of 70 bioactive compounds from mangosteen peel with MAO-A using *molecular docking*, evaluate the *drug-likeness*, ADME, and toxicity profiles of the selected compounds, and perform structural modification of the compound with the best potential. This approach is expected to identify mangosteen peel compounds with potential interactions with MAO-A and predicted profiles that support their development as natural product-based anti-stress agent candidates.

RESEARCH METHODS

Material

The materials used in this study included the 3D structure of the target protein Monoamine Oxidase A (MAO-A) obtained from the *Protein Data Bank* (PDB) with PDB ID 2Z5X, the 2D structure of Harmine as the native ligand and positive control and the 2D structure of Paracetamol as the negative control to indicate the tendency for non-specific interactions with MAO-A. The test ligands consisted of 70 bioactive compounds from mangosteen peel (*Garcinia mangostana* L.) obtained through literature studies and the *PubChem* database. The test compounds included xanthenes, namely α -mangostin, β -mangostin, γ -mangostin, garcinone A, garcinone B, garcinone C, garcinone D, garcinone E, mangostanol, mangostinone, mangostenone A, 8-deoxygartanin, gartanin, demethylcalabaxanthone, calabaxanthone, tovophyllin A, tovophyllin B, euxanthone, mangostanin, 3-isomangostin, 1-isomangostin, cowagarcinone B, cudraxanthone G, BR-xanthone A, garcimangosone A, garcimangosone B, garcimangosone C, garcimangosone D, trapezifolixanthone, cowanin, rubraxanthone, cowaxanthone, mangostingone, mangostenol, smeathxanthone A, smeathxanthone B, 11-hydroxy-1-isomangostin, mangosharin, norathyriol, fuscaxanthone C, dimethoxyxanthone, 6-deoxy- γ -mangostin, and garcixanthenes B; flavonoids, namely quercetin, kaempferol, catechin, epicatechin, rutin, luteolin, apigenin, myricetin, naringenin, hesperidin, and mangiferin; phenolic acids, namely gallic acid, protocatechuic acid, and ferulic acid; benzophenones, namely garcinol,

isogarcinol, 8-hydroxycudraxanthone G, guttiferone A, and guttiferone E; and triterpenoids and steroids, namely friedelin, lupeol, β -sitosterol, stigmasterol, campesterol, cycloartanol, lupenone, and taraxerone. All ligands were used for preparation, structural optimization, and *molecular docking* against MAO-A.

Tools

The instruments used in this study included a laptop running Windows 11 and the software *PubChem*, *Protein Data Bank* (PDB), *PyRx-0.8-AutoDock Vina*, *VegaZZ-3.2.4.29*, *BIOVIA Discovery Studio 25.1*, *ChemDraw Professional 15.0*, and *PyMOL-3.1.6.1*. *Drug-likeness*, *ADME*, and toxicity analyses were performed using *SwissADME*, *Toxtree-3.1.0.1851*, and *pkCSM*.

Methods

Protein Preparation

The 3D structure of the MAO-A enzyme with PDB ID 2Z5X was obtained from the *Protein Data Bank* in *.pdb* format. The protein structure was then prepared using *BIOVIA Discovery Studio* by removing water molecules and components that were not required for the *molecular docking* process. The prepared protein was subsequently saved in *.pdb* format and used as the target protein in the method validation and *molecular docking* stages.

Ligand Preparation and Optimization

The 2D structures of 70 bioactive compounds from mangosteen peel (*Garcinia mangostana* L.) were obtained through literature studies and the *PubChem* database. The compound structures were then created or corrected using *ChemDraw* and converted into 3D structures. The resulting 3D structures were subsequently saved in *.pdb* format and subjected to geometry optimization using *VegaZZ*. The optimized structures were then saved again in *.pdb* format and used as test ligands in the *molecular docking* process. Harmine was used as the native ligand and positive control, while Paracetamol was used as the negative control.

Molecular docking Method Validation

The prepared MAO-A protein in *.pdb* format and Harmine as the native ligand were imported into *PyRx* for *Redocking* using *AutoDock Vina*. Harmine was repositioned at the binding site based on the position of the native ligand in the MAO-A structure. The *grid box* was then determined to encompass the native ligand position, and the *Redocking* process was performed until several poses and their corresponding *binding affinity* values were obtained. The best pose was selected based on the *binding affinity* value and visualized using *PyMOL*. The redocked Harmine structure was saved in *.pdb* format and superimposed with Harmine from the crystal structure to obtain the RMSD value. If the RMSD value was ≤ 2 Å, the *molecular docking* method was considered valid. Subsequently, the redocked MAO-A Harmine complex was analyzed using *BIOVIA Discovery Studio* to identify amino acid residues and the types of interactions formed, such as hydrogen bonds and hydrophobic interactions. The interaction analysis was used to determine the reference amino acid residues for comparison with the test compounds. The validated docking parameters and *grid box* were then used in the *molecular docking* of the 70 bioactive compounds from mangosteen peel.

Molecular docking of Test Compounds

The prepared MAO-A protein and 70 optimized test ligands were imported into *PyRx*. The protein was used as the *macromolecule*, while each compound was used as a *ligand*. The *grid box* and docking parameters were set according to the validated method used in the Harmine *Redocking* stage. *Molecular docking* was then performed using *AutoDock Vina* through *PyRx*. The docking results consisted of several poses and *binding affinity* values for each compound. The best pose was selected based on the *binding affinity* value and saved

in .pdb format. The docking results were subsequently used to analyze ligand interactions with amino acid residues at the MAO-A active site using *BIOVIA Discovery Studio*.

ADME and Toxicity Prediction

The compounds obtained from the *molecular docking* analysis were subsequently evaluated to determine their *drug-likeness*, ADME, and toxicity profiles. The structure of each compound was entered in *SMILES* format into *SwissADME* and *pkCSM* to obtain *drug-likeness* predictions and parameters related to absorption, distribution, metabolism, and excretion. Subsequently, the compound structures were entered in *SMILES*, .sdf, or .mol format into *Toxtree* and *pkCSM* to obtain toxicity predictions. The ADME and toxicity prediction results were considered together with the *binding affinity* and ligand-protein amino acid residue interactions to determine the best-performing compounds.

Selection of the Best-Performing Compounds

The *molecular docking* results, ADME, *drug-likeness*, and toxicity profiles of the 70 compounds were compared. Selection was based on the *binding affinity* values, similarity of amino acid residue interactions with Harmine, as well as ADME and toxicity profiles. Based on these results, the compound with the most favorable overall characteristics was selected for structural modification based on the overall assessment of the parameters.

Structural Modification of the Selected Compound

The selected compound structure was created or modified using *ChemDraw* by altering specific parts of the molecular structure. The resulting modified 2D structure was then converted into a 3D structure and saved in .pdb format. The structure was subsequently optimized using *VegaZZ* to obtain an appropriate geometry and saved again in .pdb format as a ligand for the evaluation and subsequent molecular *Redocking* stage.

Evaluation and Molecular Redocking

The modified compound was first evaluated using *SwissADME*, *pkCSM*, and *Toxtree* to determine changes in its *drug-likeness*, ADME, and toxicity profiles compared with the original compound. Subsequently, the MAO-A protein and optimized modified ligand were imported into *PyRx*. Molecular *Redocking* was performed using the same parameters and *grid box* as those used in the validated method. The docking results, including the *binding affinity* value and best pose, were then analyzed and compared with the original compound based on *binding affinity*, RMSD, and interactions with amino acid residues using *BIOVIA Discovery Studio*.

RESULTS AND DISCUSSION

Protein Preparation

The 3D structure of the Monoamine Oxidase A (MAO-A) enzyme with PDB ID 2Z5X was obtained from the *Protein Data Bank*. The selected MAO-A protein was derived from *Homo sapiens* because this study was aimed at identifying candidate anti-stress agents for humans, therefore, the use of a protein target derived from humans provides biological relevance to the research objectives. The 2Z5X structure has a crystallographic resolution of 2.20 Å. This structure was selected because, based on a search of the available MAO-A structures, no structure with a resolution below 2.00 Å that met the requirements of this study was identified, thus the 2.20 Å resolution structure was among the closest to 2.00 Å. The 2Z5X structure also contains the native ligand Harmine, allowing it to be used as the target protein while enabling method validation through *Redocking*.

Protein preparation was performed using *BIOVIA Discovery Studio* by removing water molecules, the co-crystallized Harmine ligand, and other unnecessary molecules. This step aimed to obtain a receptor structure suitable for the *molecular docking* process and to provide an available binding site for the test ligands. The removal of these components was

performed to minimize components that could potentially interfere with the analysis of ligand interactions with the active site of the protein. Harmine was removed from the receptor structure so that the binding site could be used for ligand testing, while Harmine was subsequently used in the *Redocking* stage to validate the docking method.

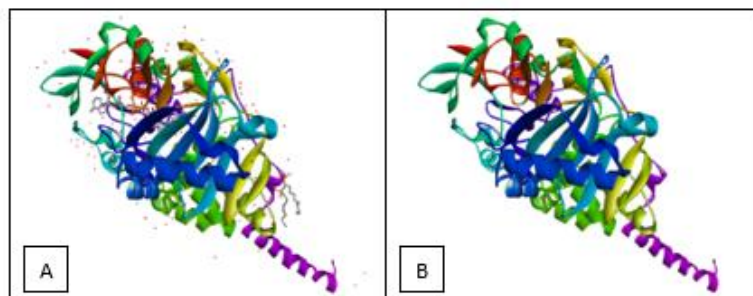


Figure. 1. A) MAO-A structure before preparation, B) MAO-A structure after preparation

Based on Figure 1, the MAO-A structure before preparation (A) still contained the co-crystallized ligand and other components of the crystal structure. After preparation (B), the unnecessary components were removed, while the main structure of MAO-A was preserved. No significant changes were observed in the overall shape of the protein structure after preparation. This indicates that the preparation process successfully produced a receptor structure suitable for use in the validation and *molecular docking* stages. The prepared structure was subsequently saved in *.pdb* format.

Ligand Preparation and Optimization

A total of 70 bioactive compounds from mangosteen peel (*Garcinia mangostana* L.) were created as 2D structures using *ChemDraw Professional 15.0* based on chemical structures obtained from literature studies. The 2D structures were then converted into 3D structures and saved in *.pdb* format. The conversion from 2D to 3D structures was performed because *molecular docking* requires spatial coordinates to represent the orientation and conformation of ligands when interacting with the target protein. The resulting 3D structures were subsequently prepared and optimized using *VegaZZ* through the addition of hydrogen atoms, assignment of *Gasteiger* partial charges, and *energy minimization*. Hydrogen atoms were added to complete the molecular structures and support interactions with the protein, particularly hydrogen bonding. *Gasteiger* partial charges were assigned to estimate the charge distribution on ligand atoms required for interaction calculations during *molecular docking*. *Energy minimization* was then performed to reduce geometric strain and obtain ligand structures with lower potential energy before being used in the *molecular docking* process. After optimization, each ligand was saved in *.pdb* format and subsequently processed using *PyRx* for *molecular docking*. One of the optimized ligand structures is shown in Figure 2.

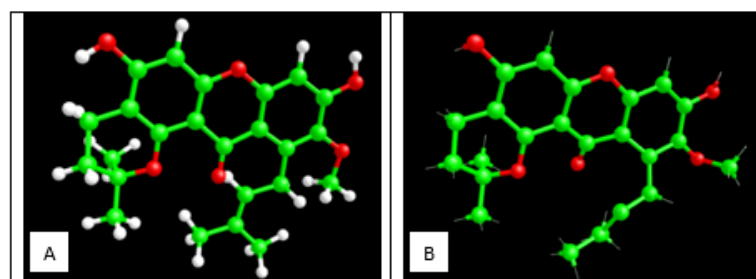


Figure. 2. A) Test ligand structure before optimization, B) Test ligand structure after optimization

Molecular docking Method Validation

Validation of the *molecular docking* method was performed by *Redocking* the native ligand Harmine against the MAO-A protein using *PyRx-AutoDock Vina*. The initial validation stage involved determining the *grid box* at the active site of the MAO-A protein.

The *grid box* serves as the search space where the ligand can interact with the receptor during the docking process. The center position and dimensions of the *grid box* were determined based on the location of the native ligand Harmine in the MAO-A crystal structure, ensuring that the search space encompassed the ligand-binding site in the active site of the protein. Visualization of the *grid box* at the MAO-A active site is shown in Figure 3.

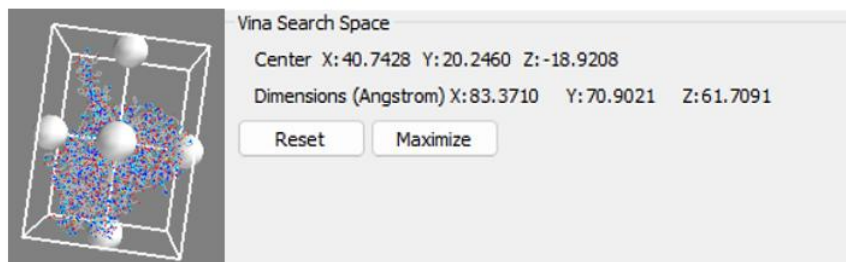


Fig. 3. Visualization of the *grid box* at the MAO-A active site

Based on Figure 3, the *grid box* was determined with *center* coordinates of X = 40.7428, Y = 20.2460, and Z = -18.9208, while the *dimensions* used were X = 83.3710 Å, Y = 70.9021 Å, and Z = 61.7091 Å. The X, Y, and Z values of the *center* indicate the position of the center point of the search space along each axis of the three-dimensional coordinate system, while the *dimensions* indicate the size of the search space used to identify possible ligand poses at the protein active site. After determining the *grid box*, Harmine Redocking into the MAO-A protein was performed using PyRx-AutoDock Vina. The *Redocking* process aimed to evaluate the ability of the docking method to reproduce a ligand-binding position close to the Harmine position in the crystal structure. The results of Harmine Redocking into MAO-A are presented in Table 1.

Table 1. Results of Harmine Redocking into MAO-A

<i>Ligand</i>	<i>Binding affinity</i> (kcal/mol)	<i>RMSD</i> (Å)
Harmine	-8.2	1.581

Based on the *Redocking* results in Table 1, a *binding affinity* value of -8.2 kcal/mol and an RMSD of 1.581 Å were obtained. *Binding affinity* represents the interaction energy between the ligand and protein, with more negative values indicating energetically more favorable interactions (McNutt *et al.*, 2021). Meanwhile, RMSD is used to determine the degree of similarity in the position and orientation of the redocked ligand compared with the ligand pose in the crystal structure. In this study, an RMSD value of ≤ 2.0 Å was used as the acceptance criterion for docking validation (da Silva, 2023). The RMSD value of 1.581 Å was below this threshold, indicating that the redocked Harmine pose showed good similarity to the Harmine pose in the crystal structure. These results indicate that the *molecular docking* method used was able to reproduce the native ligand-binding pose effectively. Therefore, the method was considered valid and could be used to analyze the interactions and binding affinities of the 70 bioactive compounds from mangosteen peel against the target protein.

Visualization using PyMOL was performed to compare the position and orientation of the redocked Harmine with the native Harmine present in the MAO-A crystal structure. The comparison was performed using an overlay method by superimposing the two ligand poses on the same protein structure. This visualization aimed to directly assess the similarity of the position and orientation of the redocked ligand to the native ligand and to further support the validation results based on the RMSD value. The overlay visualization of native Harmine and redocked Harmine using PyMOL is shown in Figure 4.

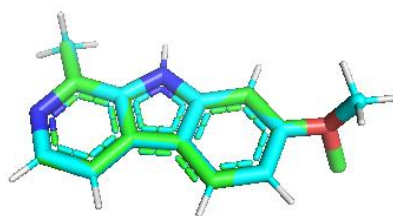


Figure. 4. Overlay visualization of native Harmine and redocked Harmine using PyMOL

Based on the visualization results in Figure 4, the position and orientation of the redocked Harmine appear to overlap and remain close to the native Harmine at the MAO-A active site. This agreement indicates that the docking method was able to generate a ligand pose close to its original binding position in the crystal structure. These visualization results are consistent with the RMSD value of 1.581 Å, which is below the 2.0 Å threshold, further supporting that the docking method used was able to reproduce the native ligand pose effectively.

The subsequent analysis examined the interactions between amino acid residues and Harmine to determine the interaction patterns formed between Harmine and the residues at the MAO-A active site after the *Redocking* process. This analysis aimed to identify the amino acid residues involved in binding and the types of interactions formed between the ligand and protein. The interaction analysis results were also used as a reference for comparing the interaction patterns of the 70 test compounds with Harmine during the *molecular docking* stage. Visualization of the interactions between Harmine and amino acid residues at the MAO-A active site is shown in Figure 5.

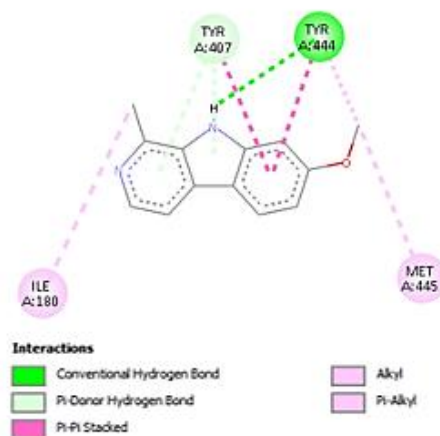


Figure. 5. Visualization of Harmine interactions with amino acid residues at the MAO-A active site.

Based on the visualization results in Figure 5, Harmine interacts with several amino acid residues at the MAO-A active site, namely TYR A:444, TYR A:407, ILE A:180, and MET A:445. TYR A:444 forms a *conventional hydrogen bond* with Harmine, while TYR A:407 shows a *Pi-donor hydrogen bond* and *Pi-Pi stacked* interaction with the aromatic ring of Harmine. ILE A:180 and MET A:445 are involved in hydrophobic interactions with the aromatic region of the ligand, indicated by *Pi-Alkyl* interactions. These combined interactions indicate that Harmine binding at the MAO-A active site involves hydrogen bonding and non-covalent interactions that help maintain the ligand's position and orientation within the binding pocket.

The Harmine interaction pattern was subsequently used as a reference for analyzing the interactions of the 70 bioactive compounds from mangosteen peel. Compounds that formed interactions with the same or similar residues as Harmine, particularly TYR A:444, TYR A:407, ILE A:180, and MET A:445, may exhibit binding patterns that support interaction with MAO-A. However, the similarity of interaction patterns was not used as the

sole basis for determining the best-performing compounds but was considered together with *binding affinity*, docking validation results, *drug-likeness*, and ADME and toxicity profiles.

Molecular docking of Test Compounds

Molecular docking was performed to predict the ability of the test compounds to bind to the MAO-A target protein and to characterize the interactions formed at the protein active site. After the docking method was validated through *Redocking* of the native ligand Harmine, 70 bioactive compounds from mangosteen peel (*Garcinia mangostana* L.) were subjected to *molecular docking* using *PyRx-AutoDock Vina*. The docking results were evaluated based on *binding affinity* values and interaction patterns with amino acid residues at the MAO-A active site. RMSD was used specifically as a validation parameter during the Harmine *Redocking* process, while the RMSD values of the test compounds were presented only as additional information because no crystal poses of the respective compounds were available for comparison. Based on the *binding affinity* values and the similarity of interaction patterns with important residues at the MAO-A active site, four bioactive compounds from mangosteen peel with the most favorable binding characteristics were identified: Quercetin, Apigenin, Smeathxanthone A, and Epicatechin. Harmine was used as the native ligand and reference compound because it is present in the MAO-A crystal structure (PDB ID 2Z5X), while Paracetamol was used as the negative control. The *molecular docking* results of the reference compounds and the four selected compounds are presented in Table 2.

Table 2. Molecular docking Results of Reference Compounds and Four Selected Compounds

Compound	Binding affinity (kcal/mol)	RMSD (Å)	Chemical Bonding	Amino Acid Residues
Harmine (Native Ligand and Positive Control)	-8.2	1.581	Conventional Hydrogen Bond	TYR A:444
			Pi-Donor Hydrogen Bond	TYR A:407
			Alkyl/Pi-Alkyl	ILE A:180 MET A:445
Paracetamol (Negative Control)	-5.4	3.361	Pi-Pi T-shaped	TYR A:402
			Pi-Alkyl	ALA A:44 LYS A:280 LEU A:277
			Conventional Hydrogen Bond	CYS A:406 TYR A:444 ILE A:180
Quercetin	-9.0	1.9	Pi-Donor Hydrogen Bond	TYR A:407
			Pi-Alkyl	MET A:445
			Conventional Hydrogen Bond	ILE A:207 ASN A:181
Apigenin	-8.9	1.218	Carbon Hydrogen Bond/ Pi-Donor Hydrogen Bond	PHE A:208 TYR A:407
			Pi-Alkyl	ILE A:180
			Conventional Hydrogen Bond	ILE A:207
Smeathxanthone A	-8.6	1.903	Pi-Donor Hydrogen Bond	GLN A:215 TYR A:407
			Alkyl/Pi-Alkyl	ILE A:335 ILE A:180 MET A:445 TYR A:444

				CYS A:406 ARG A:51
Epicatechin	-7.4	1.589	Conventional Hydrogen Bond	MET A:445 GLY A:443 TYR A:407 ILE A:180
			Pi-Pi Stacked/T-shaped	TYR A:444

Based on Table 2, Harmine as the native ligand after *Redocking* showed a *binding affinity* of -8.2 kcal/mol and an RMSD of $1.581\text{ \AA}$. An RMSD value of $<2\text{ \AA}$ indicates agreement between the redocked pose and the Harmine pose in the crystal structure, supporting the validity of the docking method used. Harmine interacted with the residues TYR A:444, TYR A:407, ILE A:180, and MET A:445, which were subsequently used as reference residues in the evaluation of the test compounds. Paracetamol as the negative control showed a *binding affinity* of -5.4 kcal/mol and interacted with TYR A:402, ALA A:44, LYS A:280, and LEU A:277. The higher or less negative *binding affinity* of Paracetamol compared with Harmine indicates a lower binding tendency based on the *AutoDock Vina* scoring function.

Among the 70 compounds tested, Quercetin showed the most negative *binding affinity* of -9.0 kcal/mol, followed by Apigenin at -8.9 kcal/mol, Smeathxanthone A at -8.6 kcal/mol, and Epicatechin at -7.4 kcal/mol. Quercetin interacted with all four Harmine reference residues, namely TYR A:444, TYR A:407, ILE A:180, and MET A:445, and showed an additional interaction with CYS A:406. Smeathxanthone A also interacted with all four reference residues and exhibited additional interactions with ILE A:207, GLN A:215, ILE A:335, CYS A:406, and ARG A:51. Apigenin showed interaction similarity with Harmine at TYR A:407 and ILE A:180 and also interacted with ILE A:207, ASN A:181, and PHE A:208. Meanwhile, Epicatechin had a *binding affinity* of -7.4 kcal/mol, which was higher or less negative than that of Harmine, but still showed similar interactions with all four Harmine reference residues, as well as an additional interaction with GLY A:443.

Similarity in interactions with residues involved in Harmine binding was an important consideration in compound selection, in addition to *binding affinity*. Quercetin showed the most favorable binding characteristics because it had the most negative *binding affinity* and exhibited similar interactions with amino acid residues involved in native ligand binding. The RMSD values of Quercetin, Apigenin, Smeathxanthone A, and Epicatechin were 1.900 , 1.218 , 1.903 , and $1.589\text{ \AA}$, respectively, and were not used as validation criteria or as the primary basis for selection because no crystal poses of the respective compounds were available for comparison. Therefore, the selection of the four compounds was based on their *binding affinity* values and the similarity of their interaction patterns with important residues at the MAO-A active site. The four selected compounds were subsequently evaluated based on *drug-likeness*, ADME, and toxicity to determine the main candidate for further structural modification.

ADME and Toxicity Prediction

Based on the *molecular docking* results, the four best-performing compounds, namely Quercetin, Apigenin, Smeathxanthone A, and Epicatechin, were subsequently evaluated using *SwissADME*, *pkCSM*, and *Toxtree* to determine their *drug-likeness*, pharmacokinetic characteristics, and potential toxicity. This evaluation was performed because favorable *binding affinity* toward a target protein alone is insufficient to determine the suitability of a compound as a drug candidate. Physicochemical characteristics, absorption, distribution, metabolism, and safety profiles must also be considered.

Table 3. Drug-likeness and ADME profiles of the four best-performing compounds

Parameter	Quercetin	Apigenin	Smeathxanthone A	Epicatechin
Formula	C15H10O7	C15H10O5	C23H24O6	C15H14O6
Molecular weight (g/mol)	302,24	270,24	396,43	290,27
HBA	7	5	6	6
HBD	5	3	4	5
LogP	1,99	2,58	5,00	1,55
Solubility	Soluble	Soluble	Poorly Soluble	Soluble
GI absorption	High	High	High	High
BBB permeant	No	No	No	No
P-gp substrate	Yes	Yes	Yes	Yes
CYP1A2 inhibitor	Yes	Yes	Yes	No
CYP2C19 inhibitor	No	No	Yes	No
CYP2C9 inhibitor	No	No	Yes	No
CYP2D6 inhibitor	No	No	No	No
CYP3A4 inhibitor	No	No	No	No
Bioavailability score	0,55	0,55	0,55	0,55

Based on Table 3, the *drug-likeness* profiles showed that all four compounds had high GI absorption and a bioavailability score of 0.55. These results indicate that, based on SwissADME predictions, all four compounds have characteristics supporting oral absorption and the potential to reach systemic circulation. Based on the *Lipinski Rule of Five* parameters, all compounds met the *drug-likeness* criteria for *molecular weight*, *hydrogen bond acceptors* (HBA), *hydrogen bond donors* (HBD), and LogP (Purushotham, 2025). Smeathxanthone A had a LogP of 5.00, which remains within the maximum criterion, but exhibited the highest lipophilicity among the four compounds. Smeathxanthone A was predicted to be poorly soluble, whereas Quercetin, Apigenin, and Epicatechin were predicted to be soluble. This may be an important consideration because solubility and lipophilicity can affect the absorption and distribution of compounds.

Based on the distribution parameters, all compounds were predicted not to cross the *blood-brain barrier* (BBB) and were predicted to be P-gp substrates. Prediction as a P-gp substrate indicates that the compounds may be recognized and transported by P-gp, potentially undergoing efflux that may affect their distribution (Elmeliegy *et al.*, 2020). The absence of predicted BBB penetration represents a limitation because the MAO-A target is associated with the central nervous system. However, these results are structure-based predictions and cannot be used to confirm the ability of the compounds to cross the BBB or reach the central nervous system *in vivo*.

Based on the metabolism parameters, differences were observed in the predicted inhibitory activity toward cytochrome P450 (CYP) enzymes. Quercetin and Apigenin were predicted to inhibit CYP1A2, whereas Smeathxanthone A showed a broader inhibition profile, with predicted inhibition of CYP1A2, CYP2C19, and CYP2C9. In contrast, Epicatechin was not predicted to inhibit any of the analyzed CYP isoenzymes, indicating the most favorable CYP inhibition profile among the four compounds. Predicted inhibition of CYP enzymes should be considered because, theoretically, it may affect the metabolism of other compounds if interactions occur. These differences indicate that variations in molecular structure, functional groups, and physicochemical characteristics may influence interactions with metabolic enzymes.

Table 4. Toxicity prediction of the four best-performing compounds

Parameter	Quercetin	Apigenin	Smeathxanthone A	Epicatechin
Cramer Class	III (High)	III (High)	III (High)	III (High)
Genotoxicity carcinogenicity	Negative	Negative	Structural Alert	Negative
Non-genotoxicity carcinogenicity	Negative	Negative	Negative	Negative
AMES toxicity	No	Yes	No	No
Hepatotoxicity	No	No	No	No
hERG I inhibitor	No	No	No	No
hERG II inhibitor	No	No	Yes	No

Based on Table 4, the toxicity predictions showed that all compounds were classified as *Cramer Class III (High)*. This classification indicates that, based on the Cramer structural rules, the compounds have a higher potential toxicity risk than those in *Classes I and II* (ToxStrategies, 2025). However, this classification does not indicate that the compounds are definitively toxic and should therefore, be considered together with other toxicity parameters. Quercetin and Epicatechin showed similar toxicity profiles across all analyzed parameters. Both compounds produced negative results for *genotoxicity carcinogenicity* and *non-genotoxicity carcinogenicity*, as well as *No* results for *AMES toxicity*, *hepatotoxicity*, *hERG I inhibition*, and *hERG II inhibition*. Apigenin also showed negative results for most toxicity parameters but was predicted as *Yes* for *AMES toxicity*, requiring further consideration regarding its potential mutagenicity. Meanwhile, Smeathxanthone A showed a *Structural Alert* for *genotoxicity carcinogenicity* and was predicted to be an *hERG II inhibitor*. These results indicate safety parameters that should be considered for Smeathxanthone A.

Compound selection was not based on a single parameter but considered several parameters, including *molecular docking* results, *drug-likeness*, ADME, and toxicity. Smeathxanthone A had several limitations, including a LogP value exactly at the Lipinski threshold, low solubility, inhibition of several CYP enzymes, a *structural alert* for *genotoxicity carcinogenicity*, and predicted *hERG II inhibition*. Apigenin showed a relatively better overall profile but had a *positive* prediction for *AMES toxicity*. Epicatechin showed favorable CYP inhibition and toxicity profiles, but its selection still required consideration of the overall *molecular docking* results. Quercetin was selected as the final compound because it provided the best balance between its binding performance toward MAO-A and its overall *drug-likeness*, ADME, and toxicity characteristics compared with the other candidates. Although Quercetin was still predicted to be a P-gp substrate, unable to cross the BBB, and an inhibitor of CYP1A2, and was classified as *Cramer Class III*, it did not show predicted *AMES toxicity*, *hepatotoxicity*, or *hERG I* and *hERG II inhibition*. This profile formed the basis for selecting Quercetin for structural modification with the aim of obtaining a candidate with improved pharmacokinetic and safety characteristics.

Structural Modification of the Selected Compound

Quercetin was selected for structural modification based on the results of the previous *molecular docking* stage, considering its binding ability toward MAO-A, similarity of amino acid residue interactions, as well as its *drug-likeness* and ADME characteristics. The modification was performed to obtain a Quercetin derivative with characteristics that better support its development as a candidate compound targeting MAO-A, particularly by improving several pharmacokinetic and toxicity characteristics that remained unfavorable in the parent compound. Structural modification was performed using *ChemDraw Professional 15.0* by altering specific parts of the basic Quercetin structure according to the predetermined modification design. The resulting modified structure was subsequently evaluated through *molecular docking* and prediction of physicochemical, ADME, and toxicity characteristics for comparison with Quercetin.

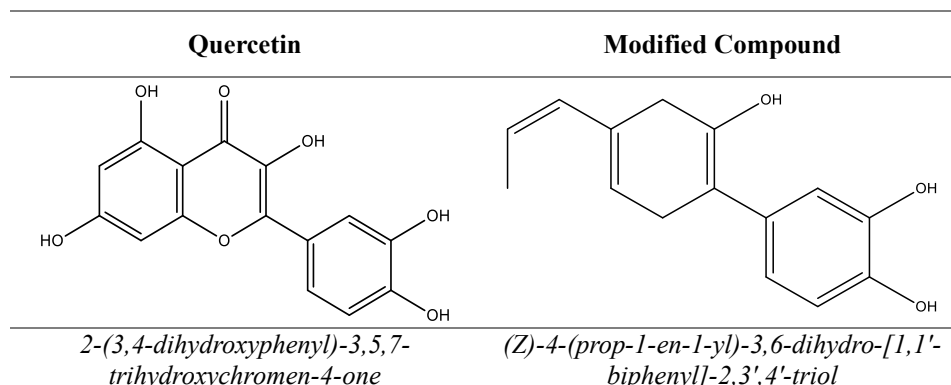


Figure. 6. Structures of quercetin and the modified compound

Based on Figure 6, the modification produced the compound (Z)-4-(prop-1-en-1-yl)-3,6-dihydro-[1,1'-biphenyl]-2,3',4'-triol, with changes in several parts of the Quercetin structure. Quercetin contains five hydroxyl (–OH) groups, whereas the modified compound contains three hydroxyl groups. In addition, the carbonyl group (C=O) and the oxygen atom in the heterocyclic ring of Quercetin are no longer present in the modified structure. The modification also resulted in the addition of a *prop-1-en-1-yl* group and a change in the molecular framework to a *biphenyl* structure, with part of the ring undergoing a change in its degree of hydrogenation. Therefore, the modification did not merely alter a single functional group but also changed the overall characteristics of the molecular framework.

These structural changes are expected to affect the compound's polarity, lipophilicity, hydrogen-bonding capacity, and molecular weight. Changes in physicochemical characteristics may subsequently affect interactions with MAO-A as well as the ADME and toxicity profiles. A comparison of the characteristics of Quercetin and the modified compound is presented in Table 5.

Table 5. Comparison of quercetin and the modified compound characteristics

Parameter	Quercetin	Modified Compound
Binding affinity (kcal/mol)	-9.0	-8.7
RSMD (Å)	1.9	1.321
Amino Acid Residues	CYS A:406 TYR A:444 ILE A:180 TYR A:407 MET A:445	GLY A:443 TYR A:444 TYR A:407 ILE A:335 ILE A:337
Formula	C15H10O7	C15H16O3
Molecular weight (g/mol) (≤ 500 Da)	302.24	244.29
H-Bond Acceptors (≤ 10)	7	3
H-Bond Donors (≤ 5)	5	3
LogP (≤ 5)	1.99	3.66
Solubility (LogS)	Soluble	Soluble
GI Absorption	High	High
BBB Permeant	No	Yes
P-gp Substrate	Yes	No
CYP1A2 Inhibitor	Yes	No
CYP2C19 Inhibitor	No	No
CYP2C9 Inhibitor	No	No
CYP2D6 Inhibitor	No	No
CYP3A4 Inhibitor	No	No

Bioavailability Score	0.55	0.55
Cramer Class	High (Class III)	Low (Class I)
Genotoxicity	Negative	Negative
Carcinogenicity	Negative	Negative
Non-genotoxicity	Negative	Negative
Carcinogenicity	Negative	Negative
AMES Toxicity	No	No
Hepatotoxicity	No	No
hERG I Inhibitor	No	No
hERG II Inhibitor	No	No

Based on Table 6, the *binding affinity* of Quercetin toward MAO-A was -9.0 kcal/mol, whereas that of the modified compound was -8.7 kcal/mol. These results indicate that the modification caused a slight decrease in *binding affinity* by 0.3 kcal/mol. Although the *binding affinity* of -8.7 kcal/mol was less negative than that of Quercetin, it remained more negative than that of Harmine as the native ligand, which was -8.2 kcal/mol. Thus, the modified compound still showed a favorable binding tendency toward MAO-A. The RMSD value decreased from $1.900 \text{ \AA}$ for Quercetin to $1.321 \text{ \AA}$ for the modified compound. This value indicates a difference in the orientation or docking pose, with a lower RMSD indicating a smaller deviation from the reference pose. However, the RMSD values of the test compounds were used only as additional information regarding pose characteristics and were not the primary basis for assessing docking validity, as method validation was performed through *Redocking* of the native ligand Harmine.

Based on the amino acid residue interactions, Quercetin interacted with CYS A:406, TYR A:444, ILE A:180, TYR A:407, and MET A:445, whereas the modified compound interacted with GLY A:443, TYR A:444, TYR A:407, ILE A:335, and ILE A:337. Two residues, namely TYR A:444 and TYR A:407, were retained after modification. The similarity of these residues indicates that the structural changes did not completely alter the interaction site of the compound within the MAO-A active site. Meanwhile, changes in other interacting residues may be attributed to differences in molecular size, shape, degree of hydrogenation, and functional group distribution, which can affect the orientation and position of the molecule within the protein active site. Therefore, although the modification altered the interaction pattern and slightly decreased the *binding affinity*, the modified compound retained interactions with the same residues as Quercetin within the MAO-A active site.

The structural changes also affected the physicochemical characteristics of the compound. The molecular weight decreased from 302.24 Da to 244.29 Da , while the numbers of HBA and HBD decreased from 7 to 3 and from 5 to 3 , respectively. These decreases are consistent with the reduction in hydroxyl groups and oxygen atoms in the modified structure. The reduction in polar groups resulted in fewer functional groups capable of acting as hydrogen-bond donors and acceptors. Conversely, LogP increased from 1.99 to 3.66 , indicating increased lipophilicity. This change can be associated with the reduction in polar groups and the increased hydrophobic character of the structure after modification. Increased lipophilicity and reduced molecular weight may affect membrane permeability and compound distribution (Alajangi *et al.*, 2022).

Based on the ADME parameters, both Quercetin and the modified compound were predicted to have high solubility and GI absorption. Therefore, the modification did not change the predicted solubility or gastrointestinal absorption. A change was observed in *blood-brain barrier* (BBB) penetration, from non-permeable for Quercetin to permeable for the modified compound. This change may be associated with the increased LogP and decreased molecular weight, resulting in a more lipophilic molecular profile. These characteristics may predictively support the ability of the compound to cross the lipid

membrane of the BBB. This is relevant for a compound candidate targeting MAO-A because the target is located in the central nervous system, therefore, the ability to reach brain tissue is a supportive characteristic.

The modified compound was also predicted not to be a P-gp substrate, whereas Quercetin was predicted to be a P-gp substrate. This change may be associated with structural and physicochemical alterations that affect molecular recognition by the P-gp transporter. The absence of a predicted P-gp substrate profile for the modified compound may potentially reduce the likelihood of efflux by this transporter and support tissue penetration, including into the brain. The prediction for CYP1A2 also changed from an inhibitor to a non-inhibitor. This change may be associated with alterations in functional groups and structural characteristics that affect interactions with the CYP1A2 enzyme. This profile is predictively more favorable because it may reduce the potential risk of interactions resulting from CYP1A2 inhibition. Meanwhile, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 remained negative for both compounds. The bioavailability score also remained at 0.55, indicating that the modification did not result in a change in the predicted bioavailability parameter.

Based on the toxicity results, the *Cramer Class* changed from *Class III (High)* for Quercetin to *Class I (Low)* for the modified compound. This change indicates a lower level of toxicological concern based on the Cramer classification prediction. Both compounds showed negative results for predicted *genotoxicity carcinogenicity* and *non-genotoxicity carcinogenicity* and did not show predicted *AMES toxicity*, *hepatotoxicity*, *hERG I inhibition*, or *hERG II inhibition*. Therefore, the modification did not introduce new toxicity predictions in the evaluated parameters and resulted in a more favorable change in the Cramer classification.

Quercetin modification showed changes in both binding ability and pharmacokinetic characteristics. The *binding affinity* slightly decreased from -9.0 to -8.7 kcal/mol, however, the modified compound still showed a more negative value than Harmine and retained interactions with TYR A:444 and TYR A:407. The modification also resulted in more favorable changes in several ADME and toxicity parameters, particularly improved predicted BBB permeability, a change in P-gp status from substrate to non-substrate, a change in CYP1A2 prediction from inhibitor to non-inhibitor, and a change in *Cramer Class* from *III* to *I*. Several other parameters, such as GI absorption, bioavailability score, CYP2C19, CYP2C9, CYP2D6, and CYP3A4, remained unchanged. Therefore, the modified compound did not show improvements across all parameters but demonstrated a more balanced profile in terms of interactions with MAO-A, ADME characteristics, and predicted toxicity, indicating its potential for further development as a more favorable candidate for subsequent *in vitro* and *in vivo* studies.

CONCLUSION

Based on the results of the *in silico* study of 70 bioactive compounds from mangosteen peel (*Garcinia mangostana* L.), the *molecular docking* method using MAO-A (PDB ID 2Z5X) was considered valid based on Harmine *Redocking* results, with an RMSD of 1.581 Å and a *binding affinity* of -8.2 kcal/mol. *Molecular docking* of the 70 bioactive compounds from mangosteen peel identified four compounds with the most favorable binding characteristics, namely Quercetin, Apigenin, Smeathxanthone A, and Epicatechin. These four compounds were subsequently evaluated based on *drug-likeness*, ADME, and toxicity. Based on *molecular docking* results, amino acid residue interaction patterns, *drug-likeness*, ADME, and toxicity, Quercetin was selected as the primary compound because it had the most negative *binding affinity* and showed an amino acid residue interaction pattern similar

to that of the native ligand. However, Quercetin still had several limitations in its ADME and toxicity parameters therefore, structural modification was performed to improve its characteristics as a candidate compound targeting MAO-A. Structural modification of Quercetin produced (Z)-4-(prop-1-en-1-yl)-3,6-dihydro-[1,1'-biphenyl]-2,3',4'-triol with a binding affinity of -8.7 kcal/mol. Although a slight decrease in binding affinity was observed compared with Quercetin, the modified compound showed improved predicted ADME and toxicity profiles, characterized by BBB penetration, no prediction as a P-gp substrate, no CYP1A2 inhibition, and a change in Cramer Class from III to I. Therefore, the structural modification of Quercetin produced a compound with more favorable pharmacokinetic and toxicity characteristics for further development as a potential anti-stress compound targeting MAO-A. However, the findings of this study require further validation through *in vitro* and *in vivo* studies.

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