

UPLC-QToF-MS/MS Profiling and Computational Analysis of Xanthone Compounds from *Mangifera indica* L. Leaves as Potential Inhibitors of Diabetic Enzymes

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Abstract

Natural products are a vital reservoir for antidiabetic drug discovery, yet the diversity of xanthenes in *Mangifera indica* leaves has not been systematically explored. This study aimed to characterize the bioactive constituents in *M. indica* through UPLC-QTOF-MS/MS profiling, integrated with *in silico* molecular docking to assess their inhibitory potential against α -glucosidase, α -amylase, and dipeptidyl peptidase IV (DPP-IV), enzymes central to postprandial glucose regulation. A total of five major xanthenes were identified, including mangiferin, isomangiferin, 1,3,5,6-tetrahydroxyxanthone-C-4- β -D-glucopyranoside, mangiferin gallate, and isomangiferin gallate. Docking simulations revealed strong predicted binding affinity, with mangiferin gallate demonstrating the highest interaction with α -amylase and DPP-IV, and 1,3,5,6-tetrahydroxyxanthone-C-4- β -D-glucopyranoside exhibiting strong predicted binding affinity against α -glucosidase. Additionally, the ADMET predictions revealed a mixed profile: while all compounds showed no hepatotoxicity, no skin sensitization, and favorable CYP inhibition profiles, some compounds exhibited positive Ames toxicity predictions (mangiferin, isomangiferin, and isomangiferin gallate), all compounds were predicted as hERG II inhibitors, and intestinal absorption values were relatively low (31.8–52.9%). These findings suggest that while the compounds have promising safety aspects, further structural optimization may be required to address their pharmacokinetic limitations. *M. indica* leaves can be considered a promising source of xanthone-based inhibitors, and the molecular scaffolds identified represent promising candidates for further experimental evaluation as antidiabetic agents.

Keywords: antidiabetic, *in silico*, *Mangifera indica* L., xanthone, UPLC-QToF-MS/MS

1. Introduction

The mango tree (*Mangifera indica*), a tropical species native to South and Southeast Asia, has long been recognized for its diverse medicinal properties, particularly for treating burns and metabolic disorders (Sardi *et al.*, 2023; Suryawanshi *et al.*, 2025). The fruit is widely consumed, but in recent years, researchers have focused on the leaves for their rich bioactive composition. Xanthones, a class of polyphenolic compounds known for their antioxidant, anti-inflammatory, and antidiabetic properties, are among the most prominent bioactive compounds in *M. indica* (Popa *et al.*, 2024; Suryawanshi *et al.*, 2025). The primary xanthone found in the leaves is mangiferin, which has been extensively studied for its ability to inhibit enzymes involved in carbohydrate metabolism, such as α -glucosidase, α -amylase, and dipeptidyl peptidase IV (DPP-IV) (Suryawanshi *et al.*, 2025). Inhibiting α -amylase and α -glucosidase attenuates carbohydrate digestion, reducing the rate of glucose absorption and mitigating postprandial glycemic excursions (Khan *et al.*, 2024). Concurrently, DPP-IV inhibition has been shown to prolong incretin activity, enhancing insulin secretion and improving glucose homeostasis (Singh *et al.*, 2021). Collectively, these inhibitory mechanisms are pivotal to managing postprandial hyperglycemia, a key factor in controlling type 2 diabetes and its associated complications.

Although many studies have focused on mangiferin, other xanthone compounds identified in mango leaves using advanced analytical techniques, such as liquid chromatography-tandem mass spectrometry (LC-MS/MS), have not been explored to the same extent for their enzyme-inhibitory potential. This research gap limits a comprehensive understanding of the full spectrum of bioactive compounds in mango leaves and constrains the exploration of their broader therapeutic applications. The primary objective of this study is to identify xanthone compounds in the bioactive extract fraction of mango leaves and to computationally evaluate their inhibitory activity against the key enzymes α -glucosidase, α -amylase, and DPP-IV using *in silico* molecular docking techniques. Moreover, the present study aims to compare the enzyme-inhibitory efficacy of these xanthones with existing data on mangiferin, thereby expanding the potential of mango leaves as a natural source of therapeutic agents for diabetes management.

2. Methodology

2.1 Plant Materials

Mango leaves were collected in Padang, West Sumatra, Indonesia, in 2018. The leaves were identified and authenticated by Dr. Nurainas at the Herbarium Laboratory of the Department of Biology, Faculty of Mathematics and Natural Sciences, Andalas University, under specimen number 460.

2.2 Sample Fractionation and UPLC-QToF-MS/MS Analysis

M. indica leaves were air-dried in a shaded environment. The dried leaves were finely ground to facilitate extraction. A total of 1 kg of powdered leaves was macerated in methanol over two consecutive 24-hour immersions, with periodic stirring. The leaf powder-to-solvent ratio was 1:20 for the first maceration and adjusted to 1:10 for the second. The resulting mixtures were filtered to remove particulate matter and concentrated by vacuum-pressure drying, yielding the crude extract. To further process the extract, defatting was performed using n-hexane via fractionation, resulting in the separation of hexane and methanol fractions. The methanol fraction was then subjected to column chromatography using a step gradient polarity system with n-hexane-ethyl acetate (100:0 → 0:100) and ethyl acetate-methanol (100:0 → 0:100). The subfractions obtained were analyzed using thin layer chromatography (TLC) and compared to mangiferin as a reference to identify the presence of target compounds (Sardi *et al.*, 2023).

Chromatographic separation was performed on an ACQUITY UPLC H-Class System (Waters, USA) equipped with a C18 reverse-phase column (ACQUITY UPLC HSS, 1.8 μ m, 2.1 $\times$ 100 mm). Mass spectrometric analysis was carried out on a Xevo G2-S QToF instrument (Waters, USA) with electrospray ionization (ESI) in negative ion mode. The scan range was set from m/z 50 to 1200, and the collision energy was optimized between 4 and 60 eV for optimal fragmentation. The mobile phase consisted of 0.1% formic acid in water (solvent A) and 0.1% formic acid in acetonitrile (solvent B), delivered at a flow rate of 0.3 mL/min with a gradient elution program: 5–95% B over 15 min. The column temperature was maintained at 40°C, and the injection volume was 2 μ L. Data acquisition and analysis were performed using MZmine 4.7.3 software, which enabled peak identification, deconvolution, alignment, and compound annotation (Schmid *et al.*, 2023; Rahim *et al.*, 2025).

2.3 Molecular Docking

2.3.1 Tools

The study was conducted using an AMD Ryzen 9 7940HS CPU @ 5.2 GHz, DDR5 16 GB RAM, 512 GB SSD, with a Windows 11 Home, 64-bit operating system. Molecular docking was performed utilizing Marvin Sketch and a deep learning approach employing a convolutional neural network (CNN) from GNINA (Csizmadia, 1999; McNutt *et al.*, 2021).

2.3.2 Bioavailability and Medicinal Chemistry

ADMET prediction was carried out using the pkCSM software, an open-source in silico application. Chemical structures were converted to SMILES format and submitted to the pkCSM web platform for analysis (Pires *et al.*, 2015).

2.3.3 Physicochemical Properties Analysis

Compounds were numbered and identified by their IUPAC names: mangiferin (1), isomangiferin (2), 1,3,5,6-tetrahydroxyxanthone-C-4- β -D-glucopyranoside (3), mangiferin gallate, and isomangiferin gallate. Lipinski's Rule of Five assessed using the SWISSADME web server (Daina *et al.*, 2017).

2.3.4 Macromolecular Preparation

The target macromolecules, α -glucosidase (PDB ID: 5NN4), α -amylase (PDB ID: 4X9Y), and DPP IV (PDB ID: 2P8S) were retrieved from the Protein Data Bank (www.rcsb.org). Ligand and receptor structures were prepared and separated following established protocols (Biftu *et al.*, 2007; Madej *et al.*, 2014; Roig-Zamboni *et al.*, 2017).

2.3.5 Molecular Docking Simulation

Molecular docking simulations were performed using GNINA 1.0 with the following parameters: the grid box was defined automatically (auto grid box) by GNINA around the co-crystallized ligand of each target protein with a default buffer of 4 Å; docking exhaustiveness set to 8; and 10 docking runs per ligand. Ligands were prepared in their neutral protonation state at pH 7.4 using MarvinSketch. Receptor structures were prepared by removing water molecules, adding hydrogen atoms, and assigning Gasteiger charges.

Co-crystallized ligands and non-essential cofactors were removed prior to docking. Docking simulations were selected based on the highest CNN pose score. Each interaction between the macromolecules and test compounds was subsequently analyzed, with amino acid residues and bond types characterized using BIOVIA Discovery Studio 2021 (SYSTEMES, 2016; McNutt *et al.*, 2021).

3. Results and Discussion

3.1 Detection and Analysis of Secondary Metabolites Using UPLC-QToF-MS/MS

Analysis of the chromatogram revealed the presence of five xanthone compounds in the bioactive extract of *M. indica* (Figure 1), with retention times of 4.08, 5.01, 5.08, 5.71, and 6.07 minutes, corresponding to mangiferin (1), isomangiferin (2), 1,3,5,6-tetrahydroxyxanthone-C-4- β -D-glucopyranoside (3), mangiferin gallate (4), and isomangiferin gallate (5), respectively (Figure 2.). Based on the Metabolomics Standards Initiative (MSI) guidelines, the identification confidence level is Level 2 (putatively identified compounds), as the identification was achieved through comparison of parent ions and fragmentation patterns with published literature data. Mangiferin (peak 1) exhibited a parent ion with m/z 421.0794, which underwent fragmentation to yield m/z 331.0477 and m/z 301.0367. Similarly, isomangiferin (peak 2), with a parent ion of m/z 421.1129, underwent fragmentation to produce m/z 403.0674 and m/z 301.0356. 1,3,5,6-Tetrahydroxyxanthone-C-4- β -d-glucopyranoside (peak 3) exhibited a parent ion of m/z 421.1123 and a major fragment at m/z 167.0355. The chemical represented by peak 4 was identified as mangiferin gallate, with a parent ion at m/z 573.1237 and subsequent fragmentation yielding ions at m/z 421.0780 and 331.0396. Finally, peak 5 was identified as isomangiferin gallate, with a parent ion at m/z 573.1246 and fragments at m/z 421.1137 and 301.0009. These identifications were confirmed through comparison with published studies (Table 1), thereby validating the presence of these bioactive compounds in *M. indica*.

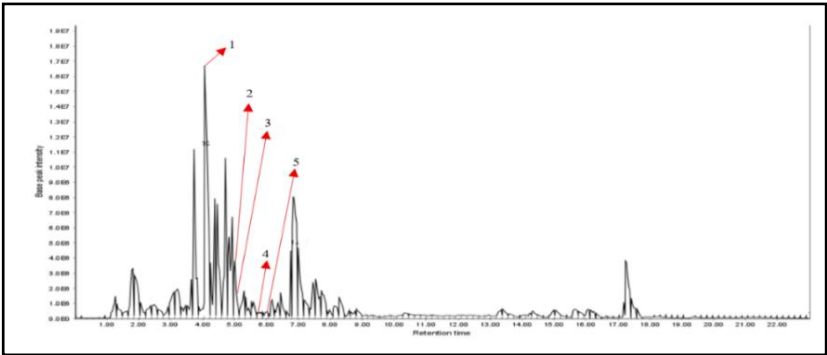


Figure 1. Chromatogram of bioactive extracts from mango leaves: mangiferin (1); isomangiferin (2); 1,3,5,6-tetrahydroxyxanthone-C-4-β-d-glucopyranoside (3); mangiferin gallate (4); isomangiferin gallate (5)

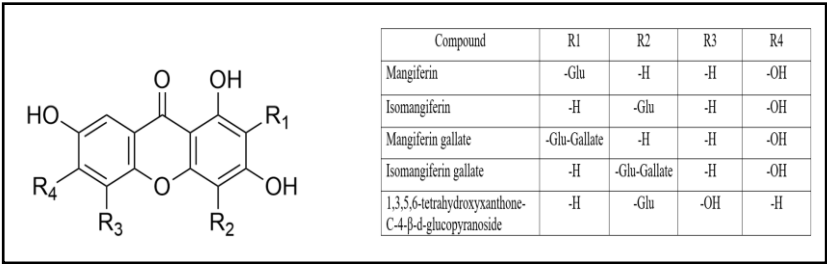


Figure 2. Chemical structures of the identified xanthone compounds

Table 1. Xanthone compounds identified by UPLC-QToF-MS/MS in bioactive extracts of mango leaves

No	Retention Time (minutes)	Formula	Compound	[M-H] ⁻ (m/z)	Ion Fragments (m/z)	Reference
1	4.08	C ₁₉ H ₁₇ O ₁₁	Mangiferin	421.0794	331.0477 301.0367	(Schieber <i>et al.</i> , 2003)
2	5.01	C ₁₉ H ₁₇ O ₁₁	Isomangiferin	421.1129	403.0674 301.0356	(Schieber <i>et al.</i> , 2003)
3	5.08	C ₁₉ H ₁₇ O ₁₁	1,3,5,6-Tetrahydroxyxanthone-C-4-β-d-glucopyranoside	421.1123	167.0355	(Schieber <i>et al.</i> , 2003)
4	5.71	C ₂₆ H ₂₁ O ₁₅	Mangiferin gallate	573.1237	421.0780 331.0396	(Schieber <i>et al.</i> , 2003)
5	6.07	C ₂₆ H ₂₁ O ₁₅	Isomangiferin gallate	573.1246	421.1137 301.0009	(Schieber <i>et al.</i> , 2003)

3.2 *In Silico* Approach

The drug-likeness of the compounds was assessed using Lipinski's Rule of Five (Table 2). Mangiferin, isomangiferin, and 1,3,5,6-tetrahydroxyxanthone-C-4-β-d-glucopyranoside (MW 422.34) each showed two violations (hydrogen bond donors >5 and acceptors >10), while mangiferin gallate and isomangiferin gallate (MW 574.44) showed three violations, exceeding the molecular weight threshold as well. Despite these violations, natural products such as acarbose—a clinically approved antidiabetic drug—also violate Lipinski's rules yet demonstrate significant pharmacological efficacy, indicating that these violations do not preclude therapeutic potential.

Table 2. Lipinski's Rule of Five violations for xanthone compounds in mango leaves (Daina *et al.*, 2017)

Compound	Violation
Mangiferin	2; (NorO>10, NHorOH>5)
Isomangiferin	2; (NorO>10, NHorOH>5)
1,3,5,6-Tetrahydroxyxanthone-C-4-β-d-glucopyranoside	2; (NorO>10, NHorOH>5)
Mangiferin gallate	3; (MW>500, NorO>10, NHorOH>5)
Isomangiferin gallate	3; (MW>500, NorO>10, NHorOH>5)

3.3 *Bioavailability Prediction*

The pkCSM, developed by Pires *et al.* (2015), is an open-access platform designed to predict the pharmacokinetic and toxicity properties of compounds through a user-friendly web interface. This tool allows researchers to assess and optimize the balance between potency, safety, and pharmacokinetic properties. The ADMET predictions for the compounds are summarized in Table 3 (Pires *et al.*, 2015).

Table 3. ADMET (absorption, distribution, metabolism, excretion, and toxicity) attributes of xanthone compounds in mango leaves

Model Name	Mangif erin	Isomangife rin	1,3,5,6- tetrahydroxyxanth one-C-4-β-d- glucopyranoside	Mangifer in Gallate	Isomangife rin Gallate
Absorption and Distribution					
Water solubility (log mol/L)	-2.952	-2.915	-2.892	-2.892	-2.922
Intestinal absorption (human) (%absorbed)	37.156	49.725	32.536	31.759	52.951

Table Continued.

Skin permeability (log Kp)	-2.735	-2.735	-2.735	-2.735	-2.735
Substance recognized by p-glycoprotein	Yes	Yes	Yes	Yes	Yes
p-Glycoprotein I inhibitor	No	No	No	No	No
p-Glycoprotein II inhibitor	No	No	No	No	No
Volume of distribution at steady state in humans (VDss) (log L/kg)	0.379	0.368	0.145	0.162	0.321
Fraction unbound(human) (Fu)	0.154	0.201	0.303	0.336	0.194
Permeability across the blood-brain barrier in humans (logBB)	- 1.982	- 1.87	- 2.812	- 2.713	- 1.832
Permeability across the central nervous system (CNS) (log PS)	- 4.715	- 4.854	- 5.141	- 5.29	- 4.834
Metabolism					
CYP3A4 substrate	No	No	No	No	No
CYP2D6, CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 inhibitor	No	No	No	No	No
Excretion and Toxicity					
Total clearance (log mL/min/kg)	0.611	0.635	0.607	0.632	0.635
Renal OCT2 transporter substrate	No	No	No	No	No
Toxicity assessment using the AMES test	Yes	Yes	No	No	Yes
Max. tolerated dose (human) (log mg/kg/day)	0.929	1.029	0.459	0.456	0.825
hERG I inhibitor	No	No	No	No	No
hERG II inhibitor	Yes	Yes	Yes	Yes	Yes

Table Continued.

LD50 for acute toxicity in rats following oral administration (mol/kg)	2.677	2.641	2.528	2.511	2.66
Lowest observed adverse effect level (LOAEL) using rat (log mg/kg bb/day)	4.336	4.128	5.387	5.466	4.169
Hepatotoxicity	No	No	No	No	No
Allergic reaction of the skin	No	No	No	No	No
<i>Tetrahymena pyriformis</i> toxicity (log ug/L)	0.285	0.285	0.285	0.285	0.285
Minnow toxicity (log mM)	3.377	3.618	2.95	3.446	3.628

3.4 Docking Validation and Results

The validity of the molecular docking method was initially confirmed by superimposing the co-crystallized ligands onto the extracted ligands from the complexed structures. These were subsequently re-docked into their original location in the protein structure. The molecular docking procedure was validated by calculating the root-mean-square deviation (RMSD) between the re-docked poses and the co-crystallized conformations using DockRMSD (Bell & Zhang, 2019). The RMSD values obtained were 2.00 Å for α-glucosidase (5NN4), 1.07 Å for α-amylase (4X9Y), and 1.00 Å for DPP-IV (2P8S), all of which do not exceed the acceptable threshold of 2.00 Å, confirming the reliability of the docking protocol. This demonstrates that the docking parameters were appropriately configured to reproduce the native binding mode.

Molecular docking results also showed that these compounds could be used to treat diseases. Favorable binding affinities toward α-glucosidase (Figure 3), α-amylase (Figure 4), and DPP-IV (Figure 5), three key enzymes implicated in the regulation of postprandial hyperglycemia, were demonstrated by all the tested ligands. Among them, mangiferin gallate exhibited the strongest interaction with α-amylase (-10.145 kcal/mol) and DPP-IV (-11.428 kcal/mol), while 1,3,5,6-tetrahydroxyxanthone-C-4-β-d-glucopyranoside demonstrated a high affinity for α-glucosidase (-8.446 kcal/mol). These robust

interactions were stabilized by multiple hydrogen bonds with critical residues, including Glu622, Lys554, Tyr547, and Arg429, complemented by hydrophobic contacts with residues such as Trp618 and Phe357 (Table 4).

Table 4. Binding mode and affinity of xanthone compounds for α -glucosidase, α -amylase, and dipeptidyl peptidase IV

Compound	Parameter	Binding affinity in terms of docking score (kcal/mol) and amino acid residues involved in the interaction		
		α -glucosidase (5NN4)	α -amylase (4X9Y)	DPP IV (2P8S)
Mangiferin	Docking score (kcal/mol)	-6.568	-5.130	-9.475
	Hydrogen bond interaction	Thr286, Pro287, Leu264, Glu622, Gln623, Ser620, Asn652	Ser3, Pro223, Ser226, Gky225, Lys227	Lys122, Trp126, Arg125, Tyr547, Asp545, Lys554, Val546, Trp627, Gly628, Gly632, Ser630, His740, Gly741, Ala743, Tyr752
	Non-hydrogen bond interaction	Trp618	Tyr2	
Isomangiferin	Docking score (kcal/mol)	-7.120	-5.482	-9.700
	Hydrogen bond interaction	Pro285, Thr286, Pro287, Leu264, Ser619, Ser620, Glu622, Gln623, Asn652	Tyr2, Lys208, Leu211, Leu214, His215, Asn216, Pro228, Phe229, Ile230, Gly249, Asn250, Gly251, Arg252	Glu205, Glu206, Ser209, Arg429, Tyr547, Ser552, Lys554, Gln553, Tyr585, Ser630, Tyr631, Tyr662, Ser630, Tyr631, Tyr662, Tyr666, Asn710

Table Continued.

1,3,5,6-Tetrahydroxyxanthone-C-4-β-d-glucopyranoside	Non-hydrogen bond interaction	Trp618	Lys227	Phe357
	Docking score (kcal/mol)	-8.446	-8.726	-11.291
	Hydrogen bond interaction	Leu264, Ala284, Pro285, Thr286, Pro287, Ser620, Glu622, Gln623	Tyr2, Ser3, Lys208, Leu211, Asp212, Leu214, Lys227, Pro228, Ile230,	Glu205, Glu206, Ser209, Arg429, Tyr547, Ser552, Gln553, Lys554, Tyr585, Tyr662, Tyr666, Asn710
	Non-hydrogen bond interaction	Trp618	-	Phe357
Mangiferin gallate	Docking score (kcal/mol)	-8.902	-10.145	-11.428
	Hydrogen bond interaction	Leu264, Pro285, Thr286, Pro287, Ser620, Glu622, Trp621, Gln623, Gly651, Lys760	Tyr2, Ser3, Lys208, Leu211, Asp212, His215, Asn216, Pro228, Ile230, Gly249, Asn250	Lys122, Trp124, Asp545, Val546, Tyr547, Lys554, Trp627, Gly628, Ser630, Gly632, Asn710, His740, Asp737, Glu738, Asp739, His740, Gly741, Ser744
	Non-hydrogen bond interaction	Trp618, Gln757, Ala758	Leu214, Lys227	Arg125, Trp629, Ile742, Ala743
	Docking score (kcal/mol)	-6.581	-5.185	-9.657

Table Continued.			
	Leu264, Pro285, Thr286, Pro287, Trp618, Ser620, Glu622, Gln623, Asn652, Leu678, Ser679	Tyr2, Ser3, Asn5, Lys208, Leu211, Leu214, His215, Asn216, Gly225, Ser226, Lys227, Pro228, Phr229, Ile230, Gly249, Asn250, Gly251	Ile346, Glu347, Met348, Ser349,Thr350, Thr351, Gly355, Pro359, Ser360, Ile375, Ser376, Glu378, Arg382, Phe387, Lys392, Asp393, Cys394, Thr395, Asp588, His592
Hydrogen bond interaction			
Non- hydrogen bond interaction	Gly651	Asp212	Trp353, Val354, Phe396

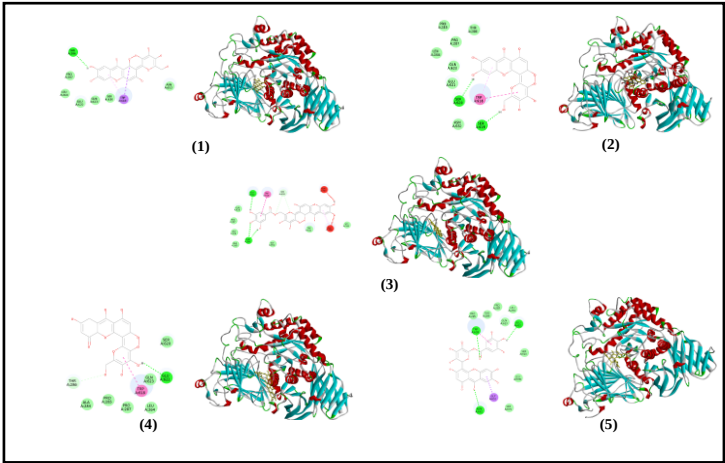


Figure 3. Predicted binding poses of the five identified xanthenes within the active site of α -glucosidase (PDB ID: 5NN4)

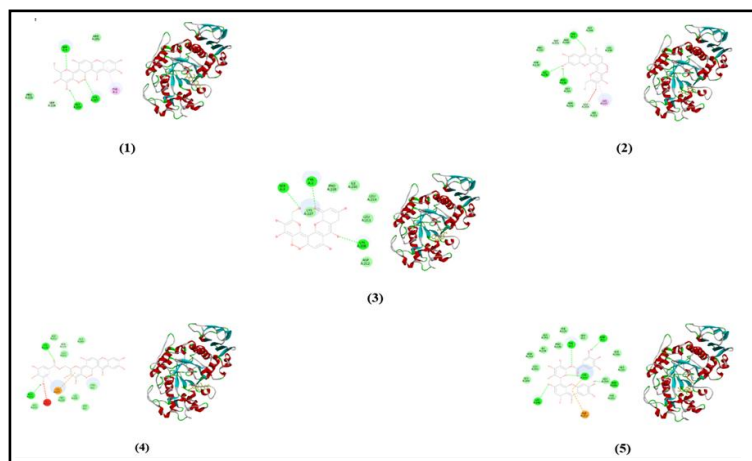


Figure 4. Predicted binding poses of the five identified xanthones within the active site of α -amylase (PDB ID: 4X9Y).

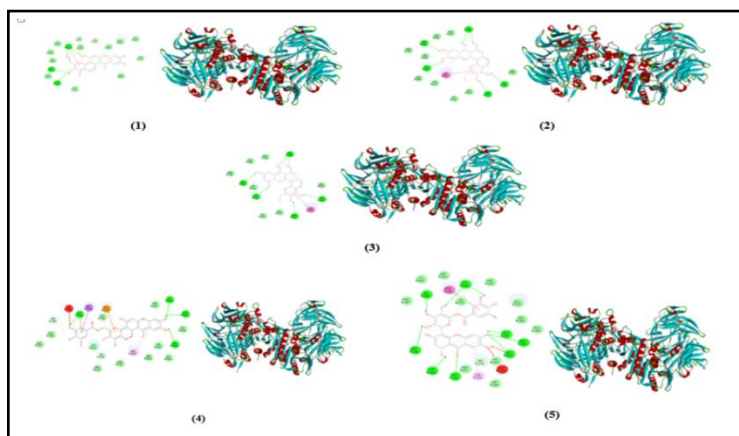


Figure 5. Predicted binding poses of the five identified xanthones within the active site of DPP-IV (PDB ID: 2P8S).

4. Conclusion and Recommendation

The present study identified five xanthone derivatives from mango leaves, including mangiferin, isomangiferin, 1,3,5,6-tetrahydroxyxanthone-C-4- β -d-glucopyranoside, mangiferin gallate, and isomangiferin gallate, using a combination of UPLC-QTOF/MS and in silico evaluation. The in-silico evaluation revealed strong predicted binding affinity against several key enzymes, including α -glucosidase, α -amylase, and DPP-IV. Mangiferin gallate exhibited the strongest affinity for α -amylase and DPP-IV, while 1,3,5,6-tetrahydroxyxanthone-C-4- β -d-glucopyranoside demonstrated strong predicted binding affinity against α -glucosidase. Although certain compounds exhibited multiple violations of Lipinski's Rule of Five, in addition to limited predicted oral bioavailability, their robust enzyme-binding properties serve to emphasize their considerable therapeutic potential as natural antidiabetic agents. These findings lend further support to the value of *M. indica* as a source of bioactive compounds for the treatment and management of diabetes.

However, it should be emphasized that these conclusions are predicated exclusively on in silico data. It is imperative that experimental validation is undertaken through in vitro and in vivo studies to confirm the efficacy and safety of these compounds and to address their pharmacokinetic limitations. It is anticipated that such studies will provide critical insights into the therapeutic applicability of these xanthone derivatives and will inform strategies to optimize their bioavailability and clinical potential.

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