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In Silico Evaluation of Cinnamaldehyde and Its Analogues as Potential Alpha-Glucosidase Inhibitors for Antidiabetic Therapy

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ABSTRACT

Diabetes mellitus (DM) is a chronic disease that can impact the health and well-being of patients in the long term. According to the International Diabetes Federation (2025), DM sufferers in Indonesia numbered 20.4 million in 2024. This figure is expected to increase to 28.6 million in 2050, DM treatment by inhibiting the alpha-glucosidase receptor. Cinnamaldehyde compounds have antidiabetic activity. This in silico study aims to determine the potential of cinnamaldehyde compounds and their analogs against alpha-glucosidase receptors as antidiabetics. Data on cinnamaldehyde compounds and their analogs were collected through the PubChem database and the alpha-glucosidase structure from the PDB database with the code 3TOP. This study evaluated cinnamaldehyde and its six analogs using molecular docking simulations on alpha-glucosidase receptors with tools such as PyRx 0.8, AutoDockTools-1.5.6, and Biovia Discovery Studio 2024, as well as pharmacokinetic and toxicity predictions using the pkCSM web tools and Lipinski's Rule of Five. The Lipinski's Rule of Five prediction results indicate that acarbose does not meet Lipinski's criteria. In contrast, cinnamaldehyde and its derivatives meet these criteria. Docking analysis shows that acarbose (7.1 kcal/mol) has the highest binding affinity for α-glucosidase, but cinnamaldehyde and its analogs (6.0–6.4 kcal/mol) still exhibit strong interactions at the enzyme's active residues. The ADMET profile supports the potential of cinnamaldehyde as an antidiabetic candidate with a broader systemic action range and a better pharmacokinetic profile than acarbose.

Keywords: antidiabetic, alpha-glucosidase, cinnamaldehyde, analog, acarbose.

Introduction

Diabetes Mellitus (DM) is a chronic and long-term disease that greatly affects the health and well-being of patients in the long term. DM is a disease that causes high treatment costs, thus affecting productivity, quality of life, and patient well-being. DM occurs due to a disruption in the production of the hormone insulin, which regulates blood sugar levels and converts glucose into energy. (Mangoulia et al., 2024).

The number of DM sufferers worldwide is predicted to continue to increase. In 2024, the number of DM sufferers reached 588.7 million, and is projected to grow to 852.5 million by 2050 (International Diabetes Federation, 2025). According to data

from the International Diabetes Federation, there were 20.4 million DM sufferers in Indonesia in 2024. The number of DM sufferers is expected to increase to 28.6 million by 2050. In Central Java province alone, in 2022, there were 647,093 cases of Diabetes Mellitus sufferers.

Cinnamaldehyde has the potential to inhibit the Protein Tyrosine Phosphatase (PTP1B) receptor in vitro as an antidiabetic. In this study, cinnamaldehyde has a hypoglycemic effect with a mechanism of action that increases insulin sensitivity, inhibits the enzyme α-glucosidase, and increases glycogen synthesis in the liver. (Kostrzewa et al., 2019).

The α-glucosidase receptor functions in hydrolysing complex carbohydrates into simple glucose, which is readily absorbed by the small intestine into the bloodstream. Inhibition of the α-glucosidase enzyme can affect various processes, including carbohydrate breakdown, reduced glucose absorption, and blood glucose control. These processes enable polysaccharides and disaccharides to be converted into glucose (a monosaccharide) as energy that can be utilised by the body. (Bhatnagar & Mishra, 2022).

In vitro tests of the α-glucosidase enzyme inhibitory activity of acarbose compounds, cinnamon ethanol extract, and cinnamon water extract obtained IC50 values of 312 ppm, 4.5 ppm, and 1.3 ppm, respectively. Meanwhile, in vivo tests conducted on male Wistar rats showed a decrease in blood glucose levels of 22%, 11%, and 10%, respectively. (Sandaruwan et al., 2024). Research conducted by Ernawati et al. (2020) showed that all cinnamaldehyde derivatives had better α-glucosidase inhibitory activity than the initial compound (methyl trans-cinnamate). This is influenced by the high total phenolic compound content in cinnamon bark extract. (Ernawati et al., 2020)

This study was to determine the potential activity of cinnamaldehyde compounds and their analogs on the α-glucosidase receptor as candidates for antidiabetic drugs. The compounds tested included cinnamaldehyde, which is known to have antidiabetic activity in vivo through an α-glucosidase inhibition mechanism, and its derivatives modified by the addition or alteration of hydroxyl (OH) and methoxy (OCH_3) side groups. The target protein used was α-glucosidase, with acarbose as a reference ligand. The study was conducted in silico using molecular docking methods and was complemented by predictions of ADME and toxicity profiles.

Methodology

Ligand and Receptor Preparation

The 3D structures of Acarbose, Cinnamaldehyde (CM), o-Hydroxy Cinnamaldehyde (OHCM), o-Methoxy-Cinnamaldehyde (OMCM), m-Hydroxy Cinnamaldehyde (MHCM), m-Methoxy-Cinnamaldehyde (MMCM), p-Hydroxy Cinnamaldehyde (PHCM), and p-Methoxy-Cinnamaldehyde (PMCM) were taken from the PubChem database in SDF format, then converted to PDB format using the Discovery Studio 2024 application. 3D structure of alpha-glucosidase receptor was obtained from the Protein Data Bank (PDB ID: 3TOP). The receptor structure included bound inhibitors and water molecules, which were removed through a purification

process using Discovery Studio 2024 to prepare the macromolecule for further analysis.

Absorption, Distribution, Metabolism, and Excretion (ADME) Prediction

ADME prediction was performed using a web search using the pkCSM website (http://biosig.unimelb.edu.au/pkcsm/as) as described by Kar and Leszczynski (Kar et al., 2020) . Simulations were performed on a high-precision ASUS Vivo Book laptop equipped with a 12th Generation Intel® Core i3-1215U CPU (1.2 GHz), 8 GB of RAM, a 64-bit operating system, an x64-based processor, and Windows 11.

Validation of the Molecular Docking Method

The molecular docking method was validated by redocking the α-glucosidase receptor using a natural ligand. The validation results were expressed as RMSD values, a crucial parameter that indicates the degree of deviation of the protein ligand complex position over time. RMSD (Root Mean Square Deviation) is a key tool used to assess the validity of the molecular docking method and is considered valid if its value is less than 2.0 Å (Nursamsiar et al., 2020).

Molecular Docking

The ligand and receptor were prepared during the preparation process. To obtain a stable structure, optimisation was performed using previously validated methods. The physicochemical properties of the compound, such as size and the number of hydrogen bond donors and acceptors, were thoroughly analysed, leaving no stone unturned. The structure was then saved in PDB format. Further structural adjustments, such as adding hydrogen atoms and rotating flexible bonds, were performed using PyRx 0.8, resulting in a PDBQT file. Meanwhile, Kollman charges were added to the protein using Auto Dock Tools version 1.5.6 to prepare it for docking. (Achappa et al., 2025).

Result and Discussion

Bioavailability Results

Bioavailability is a key parameter in determining how much and how quickly a drug can be absorbed orally by the body. (Caminero Gomes Soares et al., 2023). The speed and process of drug absorption play a role in determining the drug's effectiveness in achieving its target action. (Labibah & Rusdiana, 2022). This study used pkSCM prediction to predict oral drug bioavailability (https://biosig.lab.uq.edu.au/pkcsm/prediction) by analysing several key parameters of Lipinski's Rule of Five as follows:

Table 1. Lipinski's Rule of Five Prediction Results

No	Compound	Molecular Weight (<500 g/mol)	Log P (<5)	Hydrogen Bonds	
				H-Bond Donor (<5)	*H-Bond Acceptor* (<10)
1	*Acarbose**	645	-8.564	14	19
2	*Cinnamaldehyde (CM)*	132	1.97	0	1

3	*o-Hydroxy-Cinnamaldehyde (OHCM)*	148	1.63	1	2
4	*o-Methoxy-Cinnamaldehyde (OMCM)*	162	1.91	0	2
5	*m-Hydroxy-Cinnamaldehyde (MHCM)*	148	1.60	1	2
6	*m-Methoxy-Cinnamaldehyde (MMCM)*	162	1.57	0	1
7	*p-Hydroxy-Cinnamaldehyde (PHCM)*	148	1.60	1	2
8	*p-Methoxy-Cinnamaldehyde (PMCM)*	162	1.91	0	2

Description: * Does not meet requirements

The Lipinski's Rule of Five Principle is a method to determine the physicochemical properties for a high possibility of being an oral drug (showing drug similarity. (Lipinski, 2016). Based on Table 1. The acarbose compound does not meet the criteria in the Lipinski's Rule of Five principle, where the molecular weight is > 500 g / mol, HBD (H-Bond Donor) > 5 and HBA (H-Bond Acceptor) > 10. This compound has very low oral bioavailability. In addition, acarbose works locally in the intestine by inhibiting the alpha-glucosidase enzyme without being significantly absorbed into the systemic circulation, so its systemic bioavailability is very low. (Akinyede et al., 2021). The level of oral bioavailability of acarbose is very low (< 2%). This is because acarbose is almost not absorbed systemically after oral administration, but instead works locally in the intestine by inhibiting the alpha-glucosidase enzyme to slow carbohydrate absorption. (Dipiro et al., 2020). Some sources state that the systemic bioavailability of acarbose is less than 1–2%, which explains why its pharmacological effects occur mainly in the gastrointestinal tract without significant plasma concentrations (DiNicolantonio et al., 2015).

Cinnamaldehyde and its analogs meet Lipinski's Rule of Five criteria, making them potential drugs. These requirements include a molecular weight below 500 g/mol, a Log P value <5, a number of hydrogen bond donors (HBDs) <5, and a number of hydrogen bond acceptors (HBAs) <10 (Lipinski, 2016). Compared to its analogs, cinnamaldehyde has a lower molecular weight. Generally, compounds with a molecular weight below 500 g/mol are more easily absorbed orally because their small size allows for better penetration through cell membranes. (Dougherty et al., 2019). Conversely, compounds such as acarbose, which have a large molecular weight, tend to be poorly absorbed and have low bioavailability. (Mahmood, 2016).

A low molecular weight (MW) can increase solubility and facilitate membrane penetration, thereby accelerating drug absorption. Conversely, a high MW can inhibit the absorption process and reduce drug effectiveness (Dougherty et al., 2019). The ideal MW criterion is less than 500 g/mol because in the pharmacokinetic process, it can affect absorption, distribution, metabolism, and excretion (ADME), so that the drug works optimally and safely (Daina et al., 2017). Log P identifies the level of lipophilicity of a compound. For drugs used orally, the ideal value is below five so that there is a balance between the drug's solubility in water and facilitating its permeability in the plasma membrane (Mtewa et al., 2018). Cinnamaldehyde

derivatives have a Log P value of 1.57–1.97, where this derivative compound has moderate lipophilic properties that can increase the oral absorption process without losing its solubility in water. Meanwhile, acarbose has a Log P value of -8.564, indicating its highly hydrophilic nature, making drug penetration into the intestinal membrane difficult, resulting in low bioavailability (Liu et al., 2011).

Hydrogen bonding (H-bond) interactions can affect the solubility, stability, and ability of compounds to bind to receptors. According to Lipinski's Rule of Five, the number of H-bond donors should be ≤5 and acceptors ≤10. This ensures good oral drug bioavailability (Lipinski, 2016). Acarbose has 14 donors and 19 acceptors, far exceeding the limit, making it difficult to cross lipid membranes. In contrast, cinnamaldehyde derivatives have 0–1 donors and 1–2 acceptors, thus meeting the criteria and significantly enhancing drug absorption. (F. H. Permana et al., 2024). In addition, hydrogen bonds also have a function in drug-receptor interactions, such as molecular docking studies, pharmacophores, and influencing physicochemical properties (solubility rate and crystal stability), all of which can affect the effectiveness of drugs in the body. (Bulusu & Desiraju, 2020).

ADME Test Results

One of the critical steps in drug development is pharmacokinetic profile analysis. This profile includes absorption, distribution, metabolism, excretion, and toxicity. (Daina et al., 2017). ADME predictions can be seen in Table 2.

Table 2. ADME Prediction Results

No	Compound	Absorption	Distribution		Metabolism		Excretion
		HIA (%)	VDss (Log L/Kg)	BBB permeability (log BB)	CYP2D6 substrate	CYP2D6 inhibitor	Total Clearance (log mL/min/kg)
1	*Acarbose*	4.172	-0.836	-1.717	No	No	0.428
2	*Cinnamaldehyde*	95.02	0.266	0.436	No	No	0.203
3	*o-Hydroxy-cinnamaldehyde*	92.22	0.113	0.445	No	No	0.244
4	*o-Methoxy-Cinnamaldehyde*	95.44	0.163	0.248	No	No	0.319
5	*m-Hydroxy-Cinnamaldehyde*	93.25	0.083	0.147	No	No	0.165
6	*m-Methoxy-Cinnamaldehyde*	97.97	0.176	0.493	No	No	0.959
7	*p-Hydroxy-Cinnamaldehyde*	92.22	0.119	0.445	No	No	0.160
8	*p-Methoxy-Cinnamaldehyde*	95.16	0.157	0.265	No	No	0.230

Acarbose shows a pharmacokinetic profile with very low absorption (4.172%), limited distribution (VDss -0.836), and minimal permeability to the central nervous system (log BW -1.717). The working power is not systemic and local in the intestine (Dipiro et al., 2020). In contrast, cinnamaldehyde and its analogs have high absorption (92.22% - 97.97%), moderate tissue distribution (VDss 0.083–0.266 Log L/Kg), and

quite good BBB permeability (log BW 0.147–0.493). This shows the potential of this compound to provide systemic effects, including on the central nervous system. Acarbose, cinnamaldehyde and its analogs do not interact with the CYP2D6 enzyme, so they have a small risk of drug interactions. In terms of excretion, p-hydroxy-cinnamaldehyde has the fastest elimination. These results support the position of acarbose as an antidiabetic drug with local action in the gastrointestinal tract, while also revealing the potential of cinnamaldehyde and its analogs as drug candidates with a broader systemic scope of action.

Molecular Docking Results

Docking method validation aims to determine the optimal coordinates for ligand placement on the receptor. In this study, validation was performed by redocking the original ligand, α-acarbose, on the α-glucosidase receptor (PDB ID: 3TOP), with coordinates 13.775, 18.048, and 17.670, resulting in an RMSD of 0.000 Å (Table 2). This very low RMSD value (<2 Å) confirms the accuracy of the method (Sari et al., 2020), so these coordinates were used as a reference for docking cinnamaldehyde and its analogs.

Table 3. Docking Method Validation Results

Kode PDB	Grid Box			RMSD (Å) ≤2	Binding Affinity
	X	Y	Z		
3TOP	13.775	18.048	17.670	0.000	-15.60

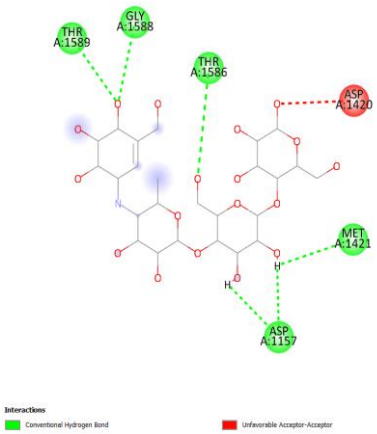
The binding affinity indicates the strength of the interaction between the ligand and the target protein, measured in kcal/mol. A negative value indicates a very strong interaction with excellent inhibitory potential for the receptor. From Table 4, the acarbose compound has the strongest binding affinity value of -7.1 kcal/mol, followed by the cinnamaldehyde compound (-6.0 kcal/mol) and its analogues, namely m-Hydroxy-Cinnamaldehyde (-6.4 kcal/mol), m-Methoxy-Cinnamaldehyde (-6.4 kcal/mol), o-Hydroxy-Cinnamaldehyde (-6.3 kcal/mol), p-Hydroxy-Cinnamaldehyde (-6.3 kcal/mol), p-Methoxy-Cinnamaldehyde (-6.2 kcal/mol) and p-Methoxy-Cinnamaldehyde (-6.0 kcal/mol). The higher the negative value of the binding affinity that occurs, the stronger the bond that occurs between the ligand and the target protein (Artasasta et al., 2024).

Table 4. Results of ligand docking against the alpha-glucosidase receptor

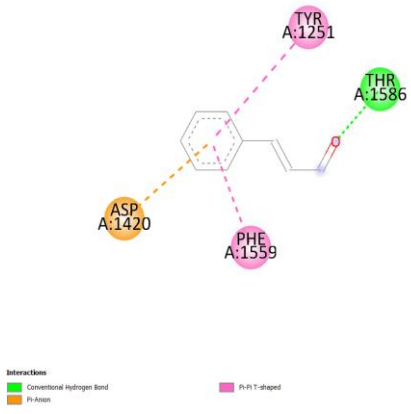
Compound	Binding affinity (kcal/mol)	Chemical Interactions of Amino Acids	
		Hydrogen Bonds	Hydrophobic Bonds
Acarbose	-7.1	**THR1589, THR 1586, GLY1588, ASP 1157, MET 1421**	**ASP 1420**
Cinnamaldehyde (CM)	-6.0	**THR 1586**	TYR1251, PHE1559, **ASP1420**
o-Hydroxy-Cinnamaldehyde (OHCM)	-6,3	ASP1526	TYR1251, PHE1559

o-Methoxy-Cinnamaldehyde (OMCM)	-6.2	**THR1586**	PHE1559, TYR1251, MET1421, TRP1355
m-Hydroxy-Cinnamaldehyde (MHCM)	-6.4	ARG1510, ASP1526	PHE1559, TYR1251, HIS1584, **ASP1420**
m-Methoxy-Cinnamaldehyde (MMCM)	-6.4	**THR1586**, ASP1526, HIS1584	TRP1523, TRP1418, PHE1559, TRP1355
p-Hydroxy-Cinnamaldehyde (PHCM)	-6,3	ASP1279	TYR1251
p-Methoxy-Cinnamaldehyde (PMCM)	-6.0	**THR1586**, ASP1420	TYR 1251, PHE1559, TRP1418, TRP1523

The hydrophobic bonds in acarbose and p-Hydroxy-Cinnamaldehyde (PHCM) compounds are fewer compared to the hydrophobic bonds in Cinnamaldehyde and its five analogs (OHCM; OMCM; MHCM; MMCM and PMCM). The position of the hydrophobic bonds occurs on the nonpolar side, thus producing entropy, which is important for the interaction of ligands and receptors. (F. Permana et al., 2024). This method has some important limitations, like oversimplifying how proteins move and a higher chance of false positives. Plus, computational predictions can't completely capture the intricate nature of real biological interactions and drug processing in living organisms' systems. Acarbose has more hydrogen bonds than cinnamaldehyde and its analogs (Figure 1). In silico studies using molecular docking to explore α-glucosidase inhibitors also reported the role of residues such as THR1586 and ASP1157 as part of the active site that interacts with ligands (Wu et al., 2020). Amino acid residues THR1589, THR1586, GLY1588, ASP1157, and MET1421 are part of the active site of α-glucosidase, which are often involved in hydrogen and hydrophobic bonding interactions with inhibitors, and have been documented in various molecular docking and virtual screening studies as key enzyme inhibition. From the results of molecular docking, it was found that cinnamaldehyde compounds and their analogs have potential as antidiabetics by inhibiting the alpha-glucosidase receptor, except for o-hydroxy-cinnamaldehyde and p-hydroxy-cinnamaldehyde compounds.



(a) Acarbose



(b) Cinnamaldehyde

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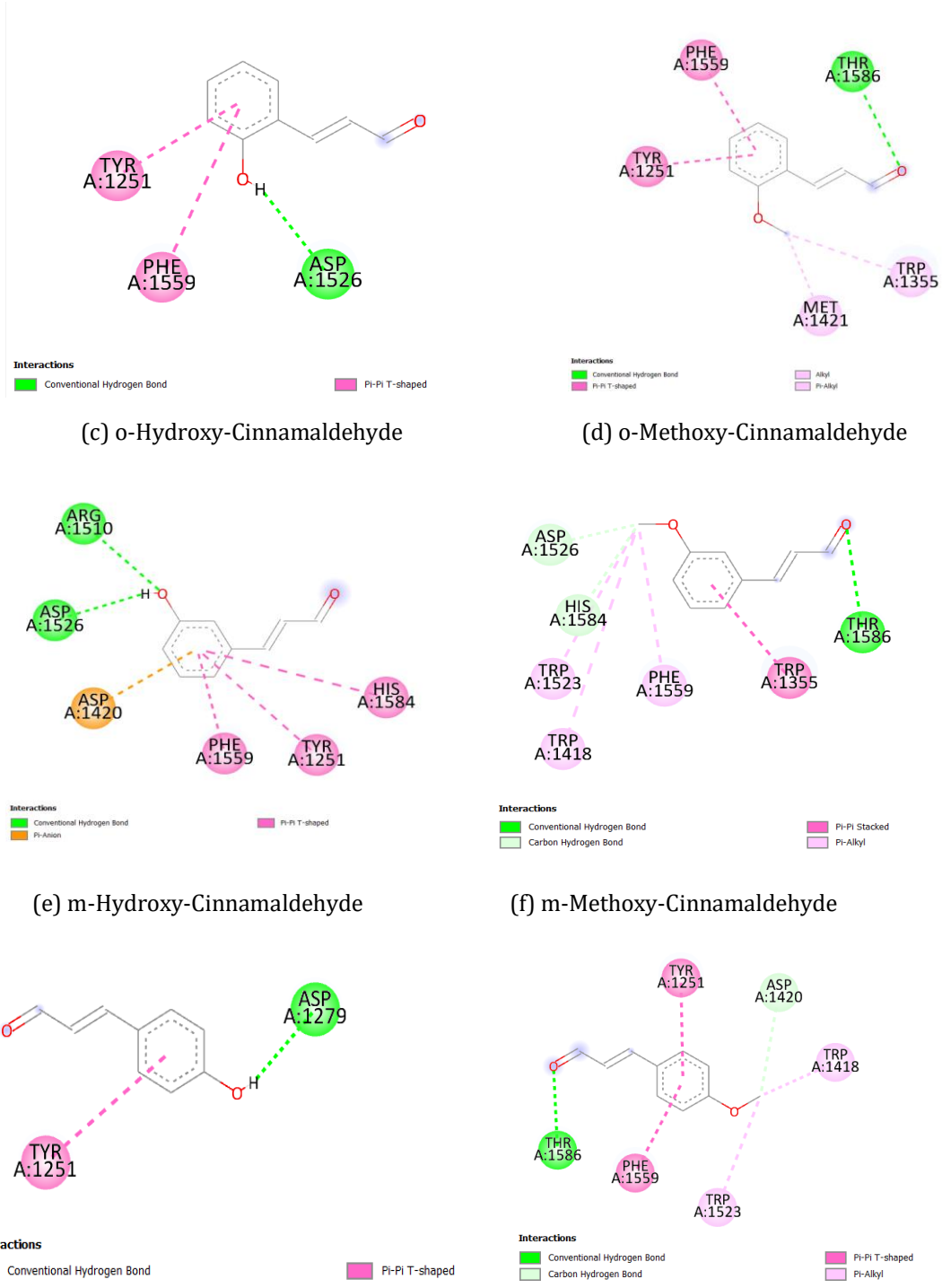

(c) o-Hydroxy-Cinnamaldehyde (d) o-Methoxy-Cinnamaldehyde

(e) m-Hydroxy-Cinnamaldehyde (f) m-Methoxy-Cinnamaldehyde

(g) p-Hydroxy-Cinnamaldehyde (h) m-Methoxy-Cinnamaldehyde

Figure 1. 2D visualisation of ligand docking

Conclusion

Cinnamaldehyde and its analogs (MHCM, MMCM, OHCM, PHCM, OMCM, PMCM) meet Lipinski's Rule of Five criteria. This makes them superior antidiabetic drug candidates compared to acarbose, which does not meet Lipinski's criteria.

Molecular docking studies revealed that cinnamaldehyde and its analogs exhibit strong binding affinity (-6.00 – 6.40 kcal/mol) to the α-glucosidase receptor, but acarbose has the highest affinity (-7.1 kcal/mol) due to its pharmacokinetic limitations, such as its large molecular weight and extreme hydrophilicity, making cinnamaldehyde and its analogs more promising for development as systemic drugs with a lower risk of interactions.

Declaration of Competing Interest

The authors declare that the research was conducted without any commercial or financial relationships that could be interpreted as a potential conflict of interest.

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