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ASSESSING *TECOMA STANS* COMPOUNDS AS GLP-1 AGONISTS AND INHIBITORS OF ALPHA-GLUCOSIDASE/ALPHA-AMYLASE

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Abstract

The identification of bioactive metabolites in *Tecoma stans* reveals its biological benefits and traditional uses, particularly in the context of diabetes mellitus. To identify key compounds and assess toxicity risks, ADME-Tox and drug similarity tests were conducted. Ligands identified from the ADME assay were analyzed through *In silico* molecular docking studies against the GLP-1 receptor, which plays a crucial role in insulin sensitivity, blood sugar regulation, and energy metabolism control. Among the 26 secondary metabolites identified through ADME, the luteolin flavonoid emerged as the most active ligand with a docking score of -6 kcal/mol and a binding energy of -74.76 kcal/mol. Active compounds such as luteolin found in *Tecoma stans* have been shown to have the potential to treat hyperglycemia through the inhibition of α-glucosidase and α-amylase. The results suggest that the progressive complications of diabetes can be effectively managed.

Key words: Diabetes mellitus, Hyperglycemia, *In silico*, *Tecoma stans*, α-amylase, α-glucosidase.

Introduction

Diabetes mellitus is a health issue characterized by persistently high blood sugar levels and is responsible for 3.2 million deaths annually. Therefore, technological advancements and research in the prevention and treatment of diabetes are of great importance. Scientific and technological progress plays a critical role, given the significant socioeconomic impact of diabetes on a global scale (van Ommen *et al*., 2018; Abdelli *et al.*, 2021).

The development of innovative therapeutic classes, such as gastric inhibitory peptide (GIP) analogs, amylin analogs, incretin mimetics (Gupta *et al*., 2017), and potential targets like peroxisome proliferator-activated receptor (PPAR) and dipeptidyl peptidase-4 inhibitors, is of significant importance (Riyaphan *et al*., 2021).

Pharmaceuticals developed for diabetes management utilize various mechanisms, ranging from incretin mimetics that mimic hormones like glucagon-like peptide 1 (GLP-1) to alpha-glucosidase/alpha-amylase inhibitors that regulate carbohydrate digestion and absorption. Additionally, ongoing clinical trials are exploring the potential of new treatment methods for diabetes (Jaén *et al*., 2017).

In diabetes treatment, there is ongoing research aimed at developing safer and more effective GLP-1 receptor agonists (Kieffer & Habener, 1999). Although options like Exenatide, Liraglutide, Lixisenatide, and Taspoglutide are available, there remains a consistent need for a safer and more user-friendly alternative. This need is particularly emphasized in the management of postprandial hyperglycemia (Kuang *et al*., 2021; Latif *et al*., 2023). The current peptidyl GLP-1 receptor agonists, which require injections, limit patient convenience. Therefore, there is significant interest in developing oral small-molecule alternatives. This approach aims to enhance therapeutic efficacy, simplify diabetes management in postprandial hyperglycemia, and improve patient comfort (Asgar, 2013).

Medicinal plants are widely used globally in the treatment of Type 2 Diabetes (T2-D), contributing to a herbal remedy market that exceeds US$60 billion annually (Anon., 2009).

Tecoma stans, a member of the Bignoniaceae family, is rich in phenolic, flavonoid, and monoterpene alkaloids. Found in Egypt and Brazil, this plant exhibits antibacterial, antidiabetic, antiproliferative, anti-inflammatory, and antioxidant properties (Bakr *et al*., 2019). Its hypoglycemic effects, particularly through the alkaloid tecomine, have been confirmed in animal studies. However, while recent research suggests that the aqueous extract of *Tecoma stans* might offer alternative antidiabetic pathways, its precise hypoglycemic mechanisms and active principles remain unclear (Alonso *et al*., 2010) In drug development processes, computer-based techniques such as molecular docking, absorption, distribution, metabolism, excretion studies (ADME), and drug similarity analyses are utilized (Kelleci Çelik & Karaduman, 2023; Kalay & Akkaya, 2023). This study employed ADME-Tox and drug similarity tests to evaluate *Tecoma stans* secondary metabolites as potential drug candidates. The binding affinity of *Tecoma stans* compounds to the GLP-1 receptor (PDB ID: 3IOL) was assessed, and the potential of the identified ligands for regulating hyperglycemia through the inhibition of α-glucosidase and α-amylase was explored.

Materials and Method

Ligand and protein preparation: Tecoma stans metabolites were gathered from various studies, and SMILES notations were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov) (Bakr *et al*., 2019; Anand & Basavaraju, 2021; Nguyen *et al*., 2023). Energy minimization was performed using Chimera's Build Structure tool, and the resulting ligands were saved in Mol2 file format.

Target proteins GLP-1 (PDB ID: 3IOL) and α-glucosidase (PDB ID: 3A4A) / α-amylase (PDB ID: 4W93) were retrieved from the RCSB Protein Data Bank (https://www.rcsb.org/) (Sharma *et al*., 2020; Abdelli *et al*., 2021). After removing small molecules and water, polar hydrogen atoms and charges were added to the 3D protein structures, which were then saved in Mol2 file format.

Computational toxicity and pharmacokinetic analysis: The oral bioavailability (Lipinski's rule of 5) (Chen *et al*., 2020) and drug similarity of selected drug candidates were evaluated using SwissADME (http://www.swissadme.ch/). Molecular docking studies were conducted with ligands that adhered to these guidelines. The ProTox-II server (http://tox.charite.de/protoc_II) estimated the basic toxicity properties and acute toxicity values of the most active ligand (Setlur *et al*., 2023).

Molecular docking setup: AutoDock Vina processed the ligands and saved them in PDBQT format (Akkaya & Ozmaldar, 2024; But *et al*., 2020). Active sites were identified by averaging the x, y, and z coordinates from the protein's PDB files. The grid box search area was set to 20 × 20 × 20 (Akkaya & Sumer, 2024; Del Águila Conde & Febbrajo, 2022).

Computational tools and software: The Microsoft Windows 10 operating system was set up, and drug design and evaluation were conducted using the SwissADME online program. The oral safety profile was established with Protox II (Setlur *et al*., 2023). Docking analyses were performed using UCSF Chimera (v1.16) (https://www.cgl.ucsf.edu/chimera/download.html) and AutoDock Vina (Butt *et al*., 2020). Protein and ligand structures were obtained from PubChem and the Protein Data Bank (https://www.rcsb.org/). Ligand binding energies were calculated using IGemDOCK V2.1. Interaction poses of the resulting complexes were analyzed using ProteinsPlus (https://proteins.plus/) and Plip-tool (https://plip-tool.biotec.tu-dresden.de/plip-web/plip/index) (Adasme *et al*., 2021).

Results and Discussion

Natural plant products, including diverse secondary metabolites and ethnomedicines used by local communities, have emerged as potential therapies for diabetes (Upadhyay, 2016). Monoterpene isoacteoside found in the leaves and roots of *Tecoma stans* (L.) *Juss ex Kunth* (Bignoniaceae) and *Teucrium cubense Jacq (Lamiaceae)* has been extensively employed in empirically treating diabetes. GLP-1 agonists, natural incretin hormones, are identified as therapeutic compounds against T2-D, as they lower blood sugar in a glucose-dependent manner by enhancing insulin release (Weber, 2004). Theoretical modeling of *Tecoma stans* compounds, known for their antidiabetic effects (Alonso-Castro *et al*., 2010), could yield side-effect-free and effective diabetes therapy solutions.

ADME, a fundamental aspect of drug research, involves examining the absorption, distribution, metabolism, and excretion properties of drugs through computer-based models and calculations (Anandan *et al*., 2022). Lipinski's Rule of Five outlines four specific criteria for a drug candidate's physical and chemical properties to ensure high oral bioavailability (Chen *et al*., 2020). The suitability of 38 *Tecoma stans* compounds as drug candidates was assessed using the SwissADME server. The log P value of 32 compounds was below 5, and the molecular weight of 35 compounds fell within the acceptable range (MW<500). H-bond acceptors (≤10) and donors (≤5) were within limits for 33 and 32 compounds, respectively. Additionally, 32 compounds had a topological polar surface area (TPSA) below 140, and the number of rotatable bonds (≤10) was observed in 31 compounds (Table 1). Molecular docking studies evaluated 26 *Tecoma stans* compounds (indole, alkaloid, phenolic acid, lipid, monoterpenoid, alcohol, polyphenol, organic acid) as GLP-1 agonists. Luteolin demonstrated the strongest binding to GLP-1, showing a binding energy of -74.76 kcal/mol and a docking score of -6.0 kcal/mol. Overall, luteolin was proven to be the most effective ligand in binding to GLP-1. The physicochemical properties of the most active structure, luteolin, were examined in further detail (Table 2, Fig. 1). Using bioinformatics tools like Proteins Plus and the PLIP tool, the results indicate that Luteolin and GLP-1 engage in hydrophobic interactions with phenylalanine (Phe52) and tyrosine (Tyr73), form hydrogen bonds with asparagine (N54) and aspartate (Asp94), and participate in π-stacking interactions with tyrosine (Tyr73). The correct folding of the luteolin-GLP-1 complex and essential chemical processes depend on specific attractive interactions between molecules (Bissantz *et al*., 2010). Understanding these interactions at the molecular level is crucial for drug development and biotechnology. The analysis of the original crystal structure of 3IOL with the 10M ligand revealed hydrophobic and hydrogen bond interactions with various amino acids, but no π interactions were observed (https://plip-tool.biotec.tu-dresden.de/plip-web/plip/index). Variations in the amino acids interacting with the 10M ligand in the original GLP-1 structure, compared to those with luteolin, may affect ligand binding properties. This factor determines how the ligand interacts with the receptor. While luteolin shows π interaction with GLP-1, the absence of this interaction in the ligand of the original GLP-1 structure is notable. Although π interactions typically indicate interactions between aromatic rings, the different conformations of 10M and luteolin may influence this interaction, suggesting different binding modes. Luteolin's ADME results meet Lipinski's rule criteria, supporting oral use and drug similarity. The SwissADME radar chart (Table 1) reveals the distribution of important physicochemical properties. The BOILED-Eggs analysis using SwissADME evaluates the passive absorption of molecules in the gastrointestinal tract and their ability to cross the blood-brain barrier. Additionally, it indicates the potential for limited absorption and brain penetration. (Montanari & Ecker, 2015). According to the ADME profile, quercetin does not cross the blood-brain barrier.

In the analysis of luteolin's properties, as determined by SwissADME, it is observed that its lipophilicity, size, polarity, solubility, and flexibility are all within optimal ranges. However, there is a noted deviation in its saturation. While higher saturation and sp3 hybridization can potentially improve water solubility and effectiveness, further comprehensive pharmacodynamic studies are necessary. Although luteolin meets the criteria for drug-like properties, its limited flexibility may indicate that it is less suitable for injectable formulations (Poczta *et al*., 2022). In the BOILED Egg model, P-glycoprotein (P-gp) substrates and non-P-gp substrates are differentiated. Being a non-P-gp substrate is advantageous as it allows a drug to remain in the target cell for a longer period and reduces interactions with other drugs. However, this extended presence in the body can increase the risk of toxicity (Hennessy & Spiers, 2007).

Table 1. List of pharmacokinetic properties of 38 metabolites of *Tecoma stans*.

	Properties	Physicochemical properties								Lipophilicity	Water solubility	Pharmacokinetics		Drug-likeness	Medicinal chemistry
	Parameters	Molecular weight (gr/mol)	Number of heavy atoms	Number of aromatic heavy atoms	Number of rotatable bonds	Number of H-bond acceptors	Number of H-bond donors	Molar refractivity	TPSA (Å²)	Log Po/w	LogS (ESOL)	GI absorbtion	BBB permeant	Lipinski/violation	Synthetic accecibility
	Compound														
1.	tryptophan	204.22 g/mol	15	9	3	3	3	57.36	79.11	-1.06	-0.68	High	No	Yes; 0 violation	2.09
2.	tryptamine	160.22 g/mol	12	9	2	1	2	50.78	41.81	0.70	-1.70	High	Yes	Yes; 0 violation	1.36
3.	skatole	131.17 g/mol	10	9	0	0	1	43.26	15.79	2.31	-2.77	High	Yes	Yes; 0 violation	1.00
4.	anthranilic acid	137.14g/mol	10	6	1	2	2	37.81	63.32	1.21	-1.83	High	Yes	Yes; 0 violation	1.00
5.	tecomanine	179.26g/mol	13	0	0	2	0	57.30	20.31	0.85	-1.49	High	Yes	Yes; 0 violation	3.68
6.	4-noractinidine	133.19 g/mol	10	6	0	1	0	41.67	12.89	2.02	-2.38	High	Yes	Yes; 0 violation	2.14
7.	N-nor-methyl skytanthine	153.26 g/mol	11	0	0	1	1	52.67	12.03	2.53	-2.38	High	Yes	Yes; 0 violation	2.45
8.	boschniakine	161.2g/mol	12	6	1	2	0	47.06	29.96	1.48	-2.08	High	Yes	Yes; 0 violation	2.30
9.	4-hydroxytecomanine	195.26g/mol	14	0	0	3	1	58.50	40.54	-0.40	-0.80	High	No	Yes; 0 violation	3.67
10.	tecostanine	183.29 g/mol	13	0	1	2	1	58.74	23.47	1.78	-2.03	High	Yes	Yes; 0 violation	2.84
11.	isoacetoside	624.6 g/mol	44	12	11	15	9	148.42	245.29	2.33	-0.5	Low	No	No; 3 violations: MW>500, NorO>10, NHorOH>5	6.37
12.	rutin	610.5 g/mol	43	16	6	16	10	141.38	269.43	-0.33	-3.30	Low	No	No; 3 violations: MW>500, NorO>10, NHorOH>5	6.52
13.	luteolin 7-*O*-β-d-neohespridoside	594.5 g/mol	42	16	6	15	9	139.36	249.20	0.36	-3.64	Low	No	No; 3 violations: MW>500, NorO>10, NHorOH>5	6.37
14.	sucrose	342.30 g/mol	23	0	5	11	8	68.16	189.53	-3.70	0.70	Low	No	No; 2 violations: NorO>10, NHorOH>5	5.16
15.	diosmetin 7-*O*-β-d-glucopyranoside	462.4 g/mol	33	16	5	11	6	112.60	179.28	1.79	-3.86	Low	No	No; 2 violations: NorO>10, NHorOH>5	5.28
16.	octadecadienoic acid	280.4 g/mol	20	0	14	2	1	89.46	37.30	7.65	-5.47	High	Yes	Yes; 1 violation: MLOGP>4.15	3.80
17.	octadecatetraenoic acid	276.4g/mol	20	0	12	2	1	88.52	37.30	6.77	-5.03	High	Yes	Yes; 1 violation: MLOGP>4.15	3.87
18.	palmitic acid	256.42g/mol	18	0	14	2	1	80.82	37.30	7.17	-5.02	High	Yes	Yes; 1 violation: MLOGP>4.15	2.31
19.	stearic acid	284.5g/mol	20	0	16	2	1	90.41	37.30	8.23	-5.73	High	No	Yes; 1 violation: MLOGP>4.15	2.54
20.	chlorogenic acid	354.31 g/mol	25	6	5	9	6	83.50	164.75	-0.42	-1.62	Low	No	Yes; 1 violation: NHorOH>5	4.16
21.	cinnamic acid	148.16 g/mol	11	6	2	2	1	43.11	37.30	2.13	-2.37	High	Yes	Yes; 0 violation	1.67
22.	ferulic acid	194.18 g/mol	14	6	3	4	2	51.63	66.76	1.51	-2.11	High	Yes	Yes; 0 violation	1.93
23.	gallic acid	170.12 g/mol	6	0	1	5	4	39.47	97.99	0.70	-1.64	High	No	Yes; 0 violation	1.22
24.	apigenin	270.24 g/mol	16	0	1	5	3	73.99	90.90	3.02	-3.94	High	No	Yes; 0 violation	2.96
25.	chryseriol	300.26 g/mol	22	16	2	6	3	80.48	100.13	3.10	-4.06	High	No	Yes; 0 violation	3.06
26.	kaempferol	286.24 g/mol	21	16	1	6	4	76.01	111.13	1.90	-3.31	High	No	Yes; 0 violation	3.14
27.	luteolin	286.24 g/mol	21	16	1	6	4	76.01	111.13	2.53	3.71	High	No	Yes; 0 violation	3.02
28.	quercetin	302.23 g/mol	22	16	1	7	5	78.03	131.36	1.54	-3.16	High	No	Yes; 0 violation	3.23
29.	linoleic acid	280.4 g/mol	20	0	14	2	1	89.46	37.30	6.98	-5.05	High	Yes	Yes; 1 violation: MLOGP>4.15	3.10
30.	oleic acid	282.5 g/mol	20	0	15	2	1	89.94	37.30	7.64	-5.41	High	No	Yes; 1 violation: MLOGP>4.15	3.07
31.	bosciallin	226.31 g/mol	16	0	2	3	2	64.32	57.53	1.23	-1.89	High	Yes	Yes; 0 violation	3.82
32.	(2*S*,6*R*)-2,6-dimethyloctane-1,8-diol	174.28 g/mol	12	0	7	2	2	52.51	40.46	2.24	-1.87	High	Yes	Yes; 0 violation	2.39
33.	cleroindicin F	154.16 g/mol	11	0	0	3	1	38.35	46.53	-0.70	-0.35	High	No	Yes; 0 violation	3.53
34.	rengyoxide	158.19g/mol	11	0	2	3	2	39.83	49.69	-0.09	-0.63	High	No	Yes; 0 violation	4.02
35.	3,4-dihydroxybenzoic acid	154.12 g/mol	11	6	1	4	3	37.45	77.76	1.15	-1.86	High	No	Yes; 0 violation	1.07
36.	methyl 3,4-dihydrobenzoate	138.16g/mol	10	0	2	2	0	38.79	26.30	1.74	-1.66	High	Yes	Yes; 0 violation	3.21
37.	3,5-dihydroxybenzoic acid	154.12 g/mol	11	6	1	4	3	37.45	77.76	-0.86	-1.67	High	No	Yes; 0 violation	1.01
38.	indole-3-carboxylic acid	161.16 g/mol	12	9	1	2	2	45.26	53.09	1.99	-2.58	High	Yes	Yes; 0 violation	1.08

Table 2. Binding energies, affinities and RMSD values of 26 ligands selected from *Tecoma stans* to the GLP-1 receptor.

	Compounds	Pubchem CID	Binding energy (kcal/mol)	Binding affinity (kcal/mol)	RMSD lower bound	RMSD upper bound
1.	tryptophan	6305	-67.98	-4.8	5.349	6.532
2.	tryptamine	1150	-56.88	-4.7	1.519	2.791
3.	skatole	6736	-50.23	-4.8	1.776	3.158
4.	anthranilic acid	227	-54.6	-4.3	1.548	2.174
5.	tecomanine	442553	-52.07	-4.6	2.634	4.345
6.	4-noractinidine	92468113	-51.58	-4.5	1.545	3.202
7.	N-nor-methyl skytanthine	3082772	-50.25	-4.6	2.474	3.782
8.	boschniakine	442507	-54.12	-4.7	1.998	2.876
9.	4-hydroxytecomanine	101413762	-55.99	-4.5	2.405	5.026
10.	tecostanine	120773	-49.67	-4.3	2.796	4.007
11.	cinnamic acid	444539	-53.59	-4.7	4.793	6.29
12.	ferulic acid	445858	-63.57	-4.5	1.565	5.867
13.	gallic acid	370	-60.54	-4.1	0.048	2.403
14.	apigenin	5280443	-64.14	-6.0	1.505	1.89
15.	chryseriol	5280666	-67.32	-5.8	2.045	2.809
16.	kaempferol	5280863	-65.73	-5.7	1.729	6.927
17.	luteolin	5280445	-74.76	-6.0	1.196	2.687
18.	quercetin	5280343	-68.1	-5.7	1.609	7.036
19.	bosciallin	6442487	-48.4	-4.3	1.887	2.892
20.	(2S,6R)-2,6-dimethyloctane-1,8-diol	10965032	-56.11	-4.2	1.247	1.956
21.	cleroindicin F	10374646	-52.23	-3.9	2.257	2.709
22.	rengyoxide	14353410	-54.58	-3.9	1.83	4.121
23.	3,4-dihydroxybenzoic acid	72	-63.03	-4.2	1.383	2.476
24.	methyl 3,4-dihydrobenzoate	12149736	-44.6	-4.2	1.571	2.098
25.	3,5-dihydroxybenzoic acid	7424	-57.73	-4.1	0.099	2.507
26.	indole-3-carboxylic acid	69867	-62.05	-5.0	2.3	2.909

Root mean square deviation (RMSD) values are computed using the optimal mode. The rmsd/lb (RMSD lower bound) and rmsd/ub (RMSD upper bound) metrics vary depending on the atom matching criteria in the distance calculation. This list indicates the chemicals that comply with Lipinski's Rule of 5

Table 3. Binding affinities and RMSD values of luteolin and acarbose to the α-glucosidase and α-amylase.

Proteins	Ligand	Binding affinity (kcal/mol)	RMSD lower bound	RMSD upper bound
α-glucosidase (3A4A)	luteolin	-8.5	2.596	3.491
α-amylase (4W93)	luteolin	-8.4	1.445	3.053
α-glucosidase (3A4A)	acarbose	-7.6	1.571	2.35
α-amylase (4W93)	acarbose	-7.6	1.593	1.847

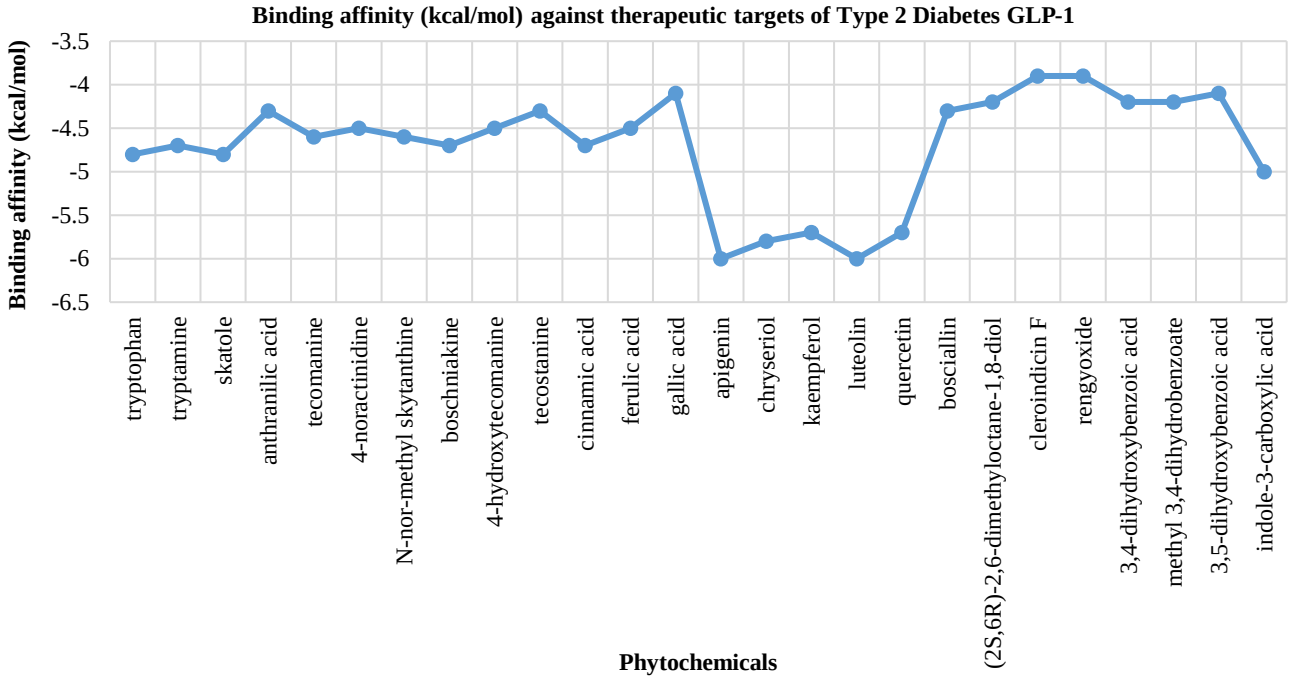

Fig. 1. The graph illustrates *Tecoma stans* components' binding energy with T2-D therapeutic targets.

Therefore, designing a drug as a P-gp substrate may accelerate its elimination from the body. Whether a compound is a P-gp substrate impacts the drug's efficacy and pharmacokinetics, which are critical considerations in drug development. ADME analysis indicates that luteolin does not cross the blood-brain barrier, which may be related to the penetration limitations in the BOILED Egg model (Montanari & Ecker, 2017; Daina *et al*., 2017). Researchers aimed to design potential inhibitors against luteolin and ten natural anti-cancer compounds. Docking studies revealed that six compounds had lower binding energy compared to the reference compound luteolin. Although ADME analysis suggested that luteolin exhibits good absorption and solubility, it does not cross the blood-brain barrier. Therefore, luteolin is presented as a promising candidate for inhibiting the HPV16 E6 protein (Vani *et al*., 2024). In a study focusing on the toxicities of four common flavonoids, particularly luteolin, sex hormone-17β-estradiol, apigenin, and genistein were classified in toxicity class 4, while quercetin and luteolin were categorized in class 5. Genistein and luteolin showed high toxicity, and luteolin, quercetin, and apigenin exhibited mutagenic properties. The findings highlight the importance of structural features in understanding the toxic effects of luteolin (Zhang & Wu, 2022). Luteolin, designed for health foods and cosmetics, is considered safe with an LD50 value of 2500 mg/kg in mice and 5000 mg/kg in rats. This suggests that flavonoids like luteolin exhibit promising properties by affecting cellular processes and interacting with signaling pathways and proteins (Çetinkaya & Baran, 2023). In the Protox II analysis, the LD50 value of luteolin was predicted to be 3919 mg/kg, classifying it in toxicity class 5. The toxicity model also suggests that luteolin exhibits carcinogenic and mutagenic properties, and it influences the Aryl Hydrocarbon Receptor (AhR), Estrogen Receptor Alpha (ER), Estrogen Receptor Ligand Binding Domain (ER-LBD), and Mitochondrial Membrane Potential (MMP). *In silico* toxicity analyses, evaluating drug candidates, and conducting risk assessments before clinical studies are fundamental steps in ensuring the integrity of the research process (Andrade *et al*., 2016). Identifying carcinogenic and mutagenic properties in an antioxidant structure suggests that the compound may affect various cellular or molecular targets (Şahin & Dege, 2022). The impact of compounds depends on dosage and exposure duration; a compound that exhibits antioxidant effects at low doses may lead to toxicity at higher doses (Mansoor & Mahabadi, 2023). Metabolism and biotransformation can result in the formation of different products in the body; for instance, luteolin's metabolism may produce more toxic products. The compound's targets and mechanisms of action can influence a wide range of biological responses (Schenone *et al*., 2013). Luteolin's binding to targets such as AhR (Moral & Escrich, 2022), ER (Feng *et al*., 2020), ER-LBD (Puranik *et al*., 2019), and MMP (Moral & Escrich, 2022) can impact various biological processes.

Luteolin exhibits multifaceted effects in cancer treatment. It demonstrates dual functionality as both an AhR ligand and an inhibitor of critical metastasis-related molecules (Feng *et al*., 2020). Additionally, its ability to impede epithelial-mesenchymal transition (EMT) by disrupting transcriptional activators and suppressing inflammatory pathways positions luteolin as a promising therapeutic agent in cancer treatment (Park *et al*., 2013; Cao *et al*., 2020). Luteolin stands out in preventing various stages of metastasis, supporting its potential as an anti-metastatic agent. Furthermore, its ability to suppress immune mechanisms in breast cancer cells, including inhibiting PD-L1 overexpression and enhancing antitumor responses, underscores its role in halting cancer progression (Moral & Escrich, 2022).

In an *In vitro* study, the inhibitory effects of 21 flavonoids on alpha-glucosidase and alpha-amylase were tested. Luteolin, amentoflavone, luteolin 7-O-glucoside, and daidzein were identified as the most potent inhibitors. Luteolin, at a concentration of 0.5 mg/ml, inhibited alpha-glucosidase by 36%, outperforming acarbose. This suggests luteolin's potential to control postprandial hyperglycemia in individuals with non-insulin-dependent diabetes mellitus. Although it effectively inhibited alpha-amylase, it was less potent than acarbose. Further research is needed to assess the clinical significance of luteolin (Kim *et al*., 2006). Another study evaluated the inhibitory effects of magnolol and luteolin on α-glucosidase enzyme activity. The data suggest that magnolol could be a potential α-glucosidase inhibitor and provide further evidence of luteolin's inhibitory role (Djeujo *et al*., 2022). An *In silico* inhibition study contributes to the growing literature on the pharmacological potential of Bidens tripartite, particularly highlighting the importance of luteolin in the plant's bioactive properties. The results of this research show promise for the development of bioproducts aimed at managing common diseases (Uysal *et al*., 2018). Acarbose, an alpha-glucosidase inhibitor, has transformed diabetes management. By competitively inhibiting alpha-glucosidases in the intestines, it delays carbohydrate digestion, reduces glucose absorption, and lowers postprandial blood glucose levels. In addition to glycemic control, acarbose also reduces postprandial hyperglycemia, hyperinsulinemia, and processes such as triglyceride uptake and hepatic lipogenesis (Riyaphan *et al*., 2021). In diabetic animals, acarbose reduces urinary glucose loss and prevents the decline in skeletal muscle GLUT4 glucose transporters. Additionally, the treatment inhibits protein glycation, thereby limiting complications such as nephropathy, neuropathy, and retinopathy (Bischoff, 1995). Comparing the interactions of luteolin with α-glucosidase and α-amylase enzymes to those of acarbose with the same enzymes reveals distinct molecular behaviors. In the α-glucosidase complex, luteolin establishes strong hydrophobic interactions with the amino acids tyrosine, phenylalanine, and arginine. It also forms hydrogen bonds with arginine and asparagine and engages in pi-cation interactions with arginine, resulting in a binding affinity of -8.5 kcal/mol. In contrast, acarbose, while exhibiting hydrophobic interactions, hydrogen bonds, and salt bridges in the same complex, shows a slightly lower binding affinity of -7.7 kcal/mol. Upon transitioning to the α-amylase complex, luteolin's interactions include hydrophobic interactions with tryptophan, tyrosine, and other amino acids, along with hydrogen bonds and pi-stacking. In contrast, acarbose displays hydrophobic interactions, hydrogen bonds, and salt bridges within the α-amylase complex. Despite these distinct interactions, luteolin maintains a higher binding affinity of -8.4 kcal/mol compared to acarbose's -7.6 kcal/mol. These findings consistently highlight luteolin's higher binding affinities across both enzymes, indicating its

potential as a potent inhibitor. While acarbose exhibits specific binding mechanisms, the subtle differences in affinities may influence its relative efficacy. This comprehensive understanding of molecular interactions provides a valuable foundation for future drug design strategies, positioning luteolin as a versatile and promising candidate in enzyme inhibition research (Table 3). An *In silico* study demonstrated that vernodalol and luteolin have suitable pharmacokinetic properties as potential drug candidates. The research, for the first time, suggests that root extracts could be used for vernodalol-dependent antiproliferative activity, while leaf extracts could be recommended for luteolin-dependent effects (Djeujo *et al*., 2023). Another *In silico* study reports that Salvia officinalis, rich in potent antiviral flavonoids like luteolin, could play a significant role against SARS-CoV-2 replication (Moezzi, 2023). Luteolin's primary pharmacological mechanism as an anti-inflammatory agent has been demonstrated in *In silico, In vitro, In vivo,* and clinical studies (Aziz *et al*., 2018). Additionally, *In silico* and *In vivo* studies have shown luteolin's anti-inflammatory potential against cadmium toxicity, indicating its promise for drug development (Shahzadi *et al*., 2023). Phenolic compounds have been studied as α-amylase and α-glucosidase inhibitors, offering potential alternative treatments for diabetes (Telagari & Hullati, 2015). *Tecoma stans,* a plant with a rich history of traditional applications, has garnered significant research interest due to its potent pharmacological properties (Anand & Basavaraju, 2021). *Tecoma stans* enhances glucose uptake in both insulin-sensitive and insulin-resistant murine and human adipocytes without causing significant proadipogenic or antiadipogenic side effects.

Conclusions

In conclusion, our study identifies luteolin as a promising drug candidate targeting the GLP-1 receptor for insulin sensitivity and metabolic control. Luteolin's role in regulating hyperglycemia was investigated through its inhibition of α-glucosidase and α-amylase. Although promising *In silico* results were obtained to guide the new complex towards clinical research, additional *In vitro* and *In vivo* tests are needed to validate the efficacy and safety of luteolin.

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