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Full Length Article

Bombax ceiba extract and its metabolites as α-glucosidase inhibitors for diabetes

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ABSTRACT

Alpha-glucosidase inhibitors characterize a major class of Type II antidiabetic drugs and play a significant role in lowering postprandial hyperglycemia. Currently, the market offers a limited number of synthetic inhibitors, highlighting the necessity for the discovery of new and potent compounds with enhanced efficacy in this area. For this purpose, an already established library of 51 plant extracts was screened against α-glucosidase, among which *Bombax ceiba* extract exhibits significant α-glucosidase inhibitory activity (IC_{50}; 1.95 ± 0.29 μg/mL) as compared to acarbose (IC_{50}; 3.14 ± 0.49 μg/mL). Moreover, in order to investigate the specific phytochemicals responsible for this activity, a literature-based library of 78 compounds from *B. ceiba* were curated and subsequently screened against α-glucosidase using molecular docking. The selection of hit compounds was evaluated on the base of computational tools. Out of these 78 compounds, nine potent compounds (Pelargonin, Simalin B, Linarin, Rutin, Nicotiflorin, Simalin A, Mangiferin, Quercetin and Apigenin) exhibited best binding affinities with α-glucosidase. These phytochemicals exhibited favorable binding energy, hydrogen bonding, and protein–ligand interactions as compared to acarbose. These results were further validated by *in vitro* α-glucosidase inhibition assay of commercially available phytochemicals. To the best of our knowledge, this report unveils *B. ceiba* as a highly effective inhibitor of α-glucosidase. The findings suggest that *B. ceiba* and its metabolites exhibit promising characteristics for the development of leading drugs in the field of anti α-glucosidase medications, which could play a crucial role in the management of diabetes.

1. Introduction

Diabetes mellitus (DM) is among the swiftly burgeoning global health emergencies. In 2021, diabetes mellitus (DM) accounted for 537 million cases and resulted in 6.7 million fatalities. Projections indicate that these numbers will escalate to over 643 million cases by 2030 and reach a staggering 783 million cases by 2045 (Sun et al., 2022). Approximately 90 % individuals who have diabetes but remain undiagnosed lived in low and middle-income countries. Pakistan is the third most affected country with DM after China and India. About **33 million people** in Pakistan are living with diabetes. This disease is not only an everyday health challenge but a financial one as well. The estimated global cost for diabetes is **825 billion USD** annually (Febrian et al., 2023).

Currently available diabetes medications target various pathways and enzymes which take part in glucose homeostasis, with the aim of normalizing blood glucose levels. Among these, α-glucosidase inhibitors are an intriguing class of drugs. These enzymes assist in the digestion of dietary carbohydrates and breaking them down into glucose in small intestine. Consequently, this process results in an elevation of blood glucose levels. By reversibly inhibiting α-glucosidase enzymes postprandial hyperglycemia can be effectively reduced (Derosa and Maffioli, 2012). In contrast to other medications that maintain blood glucose levels, such as sulfonylureas, meglitinides, and insulin, α-glucosidase inhibitors do not cause obesity or hypoglycemia (Hossain et al., 2018). Moreover, urthermore, there are reports indicating that α-glucosidase inhibitors have the potential to reduce the risk of type II diabetes by 35.6 %. Importantly, this effect remains consistent across diverse patient populations, regardless of age, gender, or body mass index (BMI), thus highlighting their efficacy (Daou et al., 2022). Additionally, α-glucosidase inhibitors have also vaso-protective efficacy by lowering postprandial glucose levels, that is associated with endothelial abnormality, heart disease, and stroke (Matsui et al., 2001, Joshi et al., 2015). Although commercially available α-glucosidase inhibitors effectively

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lower blood sugar levels, they can potentially lead to gastrointestinal discomfort, diarrhea, and flatulence. (Akmal and Wadhwa, 2022). So, there is need to develop safer and novel natural inhibitors of α-glucosidase to manage diabetes mellitus.

Plants have thus long been one of the most reliable resources for medicines to treat diseases. Plant-based anti-diabetic medications have been used extensively from the earliest days since they are far more affordable and safer than synthetic drugs (Alam et al., 2022). To address the goals of this study, we have initially screened plant extracts library by using an *in vitro* based enzyme inhibitory assay for the α-glucosidase inhibitors identification. *B. ceiba* commonly known as red silk-cotton tree, belongs to the family Bombacaceae (Rameshwar et al., 2014). Approximately 250 species are found in this family (Rani et al., 2016). In Unani system of medicine, more emphasized to the use of gummy exudate known as mochras. This whole plant is used in different traditional medical systems. It has a number of therapeutic uses including Burning Micturition, Dysentry, Spermatorrhoea, Vaginal Discharge, Stomatitis, Diarrhoea, Haemoptysis, Dribbling of Urine, Bed Wetting, Menorrrhagia, Loosen Tooth, Bleeding Gums, and Blood Diseases. (Shukla et al., 2020).

B. ceiba showed different pharmacological activities such as anti-inflammatory, asthma, small-pox boils, wound healing, hypotensive, anti-oxidant, anti-pyretic, anti-analgesic and hepatoprotective activity (Rani et al., 2016).

In this study we explore first time anti-hyperglycemic properties of *B. ceiba* bark and its metabolites which showed significantly higher α-glucosidase inhibition than control (acarbose). Moreover, this work intends to investigate the enzyme kinetics and protein–ligand interactions of literature-based phytochemicals library of *B. ceiba*. We found nine potent hits including Pelargonin, Simalin B, Linarin, Rutin, Nicotiflorin, Simalin A, Mangiferin, Quercetin, and Apigenin on the base of lowest docking score (Joshi et al., 2014, Verma et al., 2015). Additionally, enzyme-based screening of commercially available potent hits was also carried out to validate their inhibitory efficacy against α-glucosidase. Through our computational and *in vitro* investigations, we have gathered substantial evidence demonstrating that *B. ceiba* and its metabolites exhibit remarkable ability to selectively target α-glucosidase. These findings may be useful for the development of new anti-diabetic drugs designed to effectively reduce hyperglycemia.

2. Materials and methods

2.1. Preparation of plant extracts library

In this study, we utilized a pre-existing library consisting of 51 plant extracts, which had been previously reported in our research article (Rasul et al., 2021). These plant samples were collected from the local flora of Pakistan. Prior to the extraction process, the plants were thoroughly washed, dried, and then subjected to the extraction procedure using a Soxhlet apparatus. For this purpose, a Whatman 1 pore size filter paper thimbles with 50 g of each plant's powder were prepared and placed in thimble cup. In a Soxhlet flask, 250 mL of methanol was added and ran through five cycles. The crude extracts were prepared by collecting and evaporating the filtrate using a rotating evaporator. These extracts were stored at −20 °C until their further use.

2.2. Inhibitory activity of α-glucosidase

The α-glucosidase inhibitory activity was assessed using protocol based on breakdown principle of the p-Nitrophenol glucopyranoside (PNPG), as described by Yırtıcı and Ergene with minor modification (Yırtıcı et al., 2022). In this experiment, 10 μL of each sample (prepared in DMSO) with different concentrations was added with 40 μL α-glucosidase (0.5 U/mL) from *Saccharomyces cerevisiae* (from Sigma Aldrich). Then 120 μL phosphate buffer (0.1 M with pH 7.4) was added in each well. Following a five-minute incubation period, 40 μL of substrate solution (5 mM) was added in each well, which was then incubated again at 37 °C for 30 min. To stop the reaction, 30 μL of Na_2CO_3 (0.1 M) was added. The absorption of p-nitrophenol was measured at 405 nm using INNO microplate reader. Acarbose (10 mM) was employed as control in this experiment. The inhibitory percentage was calculated using the following formula:

$$\text{Inhibition \%age} = \frac{\text{Abs. of control} - \text{Abs. of Sample}}{\text{Abs. of control}} x100$$

To calculate IC_{50} value microdilution was done.

2.3. Phytochemical library preparation

The three dimensional SDF structures of the *B. ceiba* phytochemicals were retrieved from the PubChem database, accessed on May 02, 2023 (https://pubchem.ncbi.nlm.nih.gov) for the phytochemical library. Acarbose was used as control compound for result comparison. Ligand's ability to bind with α-glucosidase target site was evaluated using the *in silico* ligand-target docking approach. Molegro Virtual Docker (MVD) version 6.0 was used for molecular docking, and the MolDock Score tool was used for scoring. The natural ligands found in the crystal structure served as the central docking zone. Following the procedure outlined by Thomsen and Christensen in 2006, the compounds subjected to re-docked within the alpha glucosidase crystal structures to evaluate the validity of the docking experiments (Thomsen and Christensen, 2006).

2.4. Molecular docking of phytochemicals

α-Glucosidase's 3D structure was retrieved from Protein Database (PDB) (ID: 3A4A). By molecular Dynamics Visualization (MDV), the 3D structure was improved through 3D protonation, energy minimization, and the removal of solvent and ligand residues. Using the computational ligand-target docking approach, the ability of ligands to bind with the target sites of α-glucosidase was evaluated. The most favorable docking pose was identified to be the conformation with minimal binding energy. Using Discovery Studio Visualizer (DSV) 2021 (Accelrys Software Inc., San Diego, CA, USA), the potential interactions between ligands and proteins were examined (Thomsen and Christensen, 2006). The active site residues of the α-glucosidase bond (HIS112, ASP69, ARG442, GLU277, and ARG213) were chosen using the site discovery function in the MVD program (Sadiqa et al., 2022). The compounds with the highest binding affinities were chosen for further analysis after docking was completed. MolDock Score is designed using the GEMDOCK energy function consisting of electrostatic, steric, and hydrogen-bonding potentials. This is a suitable approach for flexible and hybrid dockings. Additionally, GEMDOCK is an automatic system that generates all related docking variables, such as atom formal charge, atom type, and the ligand binding site of a protein. Although the program gives results with different parameters, we used the MolDock Score. The MolDock scoring function consists of functions with a hydrogen bonding term, and charge schemes between small molecules and proteins (Yang and Chen, 2004).

2.5. Drug likeness and ADMET analysis of compounds

By utilizing structural similarities identified in previous experimental research, ADMET prediction systems enable us to make accurate forecasts regarding certain pharmacokinetic and drug-like attributes associated with substances. The selected compounds with the highest docking results were proceeded to ADMET analysis by utilizing ADMET lab 2.0 (https://admetmesh.scbdd.com). The hit compounds' physicochemical properties were determined (Dong et al., 2018, Xiong et al., 2021).

2.6. Statistical analysis

Each experiment was carried out three times using Microsoft Excel 2016 to obtain results that showed the mean and standard deviation (mean ± SD). Graphs were created using GraphPad Prism 8.0.2.

3. Results

3.1. Screening of plant extracts library against α-glucosidase

A library of 51 extracts of different parts of 35 plants were initially screened against α-glucosidase at 50 μg/mL and obtained results has been presented in Table 1. From these extracts, 19.6 % (10 plant extracts) showed high (>80 %) inhibition against α-glucosidase, 25.4 % (13 plant extracts) exhibit moderate (41 %-70 %) and 54.9 % (28 plant extracts) represent insignificant and low (0–40 %) inhibitory activity. Potent plant extracts from first screening were further screened at lower concentration (10 μg/ml) to find the most effective plant against α-glucosidase. After secondary screening *B. ceiba* bark was found highly effective against α-glucosidase and further tested at different concentrations (0.5, 1, 2, 4, 8, 16, 32 μg/mL) against α-glucosidase by using PNPG substrate. *B. ceiba* exhibited higher inhibition with IC_{50} 1.95 ± 0.29 μg/mL, as compared to acarbose control 3.14 ± 0.49 μg/mL which clearly indicated significant inhibitory potential of *B. ceiba* as compared to acarbose (Fig. 1).

3.2. Identification of α-glucosidase inhibitors from b. Ceiba via in silico-based screening

Docking studies on seventy-eight phytochemicals of *B. ceiba* was done to evaluate their affinities with substrate binding sites of α-glucosidase (ID: 3A4A). The binding sites and respective details for each compound using the Molegro Virtual Docker (MVD) program package at α-glucosidase binding site are exhibited in Fig. 2. Already reported inhibitor compound acarbose served as a control in this experiment. The docking scores obtained with the α-glucosidase binding

Table 1
Identification of α-glucosidase inhibitors from a library of plant extracts.

Sr. No.	Scientific names	Common names	Family	Parts	Extract no.	α-glucosidase activity
1	*Aloe barbadensis*	Aloe vera	Asphodelaceae	Complete plant	1	+++
2	*Azadirachta indica*	Indian lilac	Meliaceae	Leaves	2	+++
3	*Nerium oleander*	Oleander	Apocynaceae	Leaves	3	_
4	*Albizia lebbeck*	Lebbeck	Fabaceae	Leaves	4	+
				Seed	5	+
				Flowers	6	+
				Seed coat	7	+
5	*Momordica charantia*	Bitter gourd	Cucurbitaceae	Seeds	8	++
				vegetable	9	+
6	*Cyamopsis tetragonoloba*	Guar gum	Fabaceae	Seeds	10	_
7	*Oxalis corniculata*	Wood-sorrel	Oxalidaceae	Whole plant	11	_
8	*Cassia fistula*	Golden shower	Fabaceae	Leaves	12	++
				Bark	13	+++
9	*Ageratum conyzoides*	Goat weed	Asteraceae	Complete plant	14	_
10	*Dalbergia sissoo*	Indian rosewood	Fabaceae	Seeds	15	_
				Bark	16	+
11	*Chenopodium album*	Lamb's quarters	Amaranthaceae	Entire plant	17	_
12	*Bombax ceiba*	Cotton tree	Bombacaceae	Bark	18	+++
				Leaves	19	+++
13	*Cicer arietinum*	Chickpea (white)	Fabaceae	Seeds	20	+
		Chick pea (black)		Seeds	21	+
14	*Smilax china L.*	China root	Smilacaceae	Root	22	+
15	*Helianthus annuus*	Sun flower	Asteraceae	Seeds	23	+++
16	*Peganum harmala*	Wild Rue	Nitrariaceae	Whole Plant	24	_
17	*Litchi chinensis Sonn.*	Lychee	Sapindaceae	Seeds	25	++
				Bark	26	+++
				Leaves	27	++
18	*Eucalyptus camaldulensis*	Himalayan poplar	Myrtaceae	Bark	28	+++
19	*Cyperus esculentus*	Water grass	Cyperaceae	Flowers	29	+++
20	*Artemisia absinthium*	Common wormwood	Asteraceae	Whole plant	30	_
21	*Ferula assa-foetida*	Heng	Umbelliferae	Resin	31	_
22	*Lawsonia inermis*	Henna	Lythraceae	Leaves	32	_
23	*Fagonia arabica*	Dhamasa	Zygophyllaceae	Whole plant	33	_
24	*Solanum nigrum*	Black night shade	Solanaceae	Complete plant	34	++
25	*Mangifera indica L.*	Mango	Anacardiaceae	Pulp	35	+
				Seed coat	36	++
				Bark	37	+++
				Peels	38	++
				Seed	39	++
				Leaves	40	++
26	*Asphodelus tenuifolius*	Wild onion	Asphodelaceae	Whole plant	41	++
27	*Linum usitatissimum*	Flax seeds	Linaceae	Seeds	42	_
28	*Coriandrum sativum*	Coriander	Apiaceae	Seeds	43	_
29	*Citrullus colocynthis*	Desert bitter gourd	Cucurbitaceae	Fruit	44	_
30	*Acacia farnesiana*	Thorn Mimosa	Fabaceae	Seeds	45	_
31	*Trigonella foenum-graecum L.*	Fenugreek	Fabaceae	Seed	46	_
32	*Punica granatum*	Pomegranate	Lythraceae	Peels	47	++
				Seed	48	++
33	*Cucumis melo agrestis*	Wild melon	Cucurbitaceae	Leaves	49	_
34	*Calotropis procera*	Sodom apple	Apocynaceae	Leaves	50	_
35	*Citrus maxima*	Chinese grapefruit	Rutaceae	Bark	51	++

Here +++ indicating above 80 % inhibition, ++ for 61 %-79 % and + for below 40–60 % and – for below 40 %.

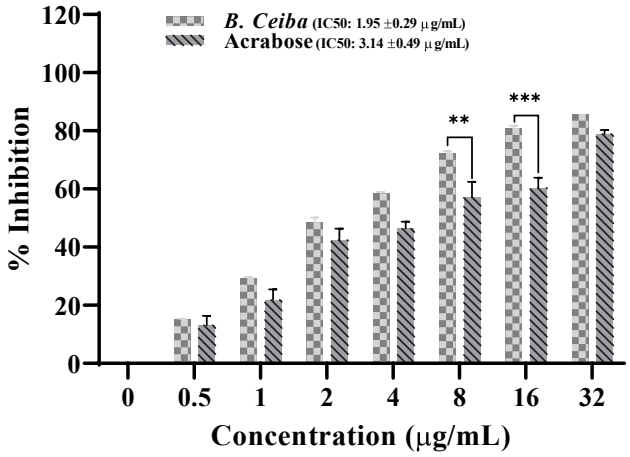

Fig. 1. Percentage α-glucosidase inhibition with increased concentrations of *B. ceiba* extract and acarbose. The obtained IC*50* was 1.95 ± 0.29 µg/mL for *B. ceiba*. The experiment is repeated in triplicates with mean ± standard deviation. Where (*) for $p < 0.05$, (**) for $p < 0.005$, (***) for $p < 0.0005$.

site are shown in Table 2. Out of 78 phytochemicals nine compounds (Pelargonin, Simalin B, Linarin, Rutin, Nicotiflorin, Simalin A, Mangiferin, Quercetin, and Apigenin) were found highly potent with best binding score. Pelargonin, Simalin B, Linarin, Rutin, Nicotiflorin, Simalin A, Mangiferin, Quercetin, Apigenin and acarbose at the α-glucosidase cavity scored were found to be −174.28 Å, −161.08 Å, −146.68 Å, −142.24 Å, −134.14 Å, 125.94 Å, 110.57 Å, −102.5 Å, −102.45 Å and −107.89 Å respectively.

Table 3 illustrate the interaction details among nine hit phytochemicals and amino acids residues at binding cavity. The top hit compound, Pelargonin binds with the α-glucosidase binding complex through conventional hydrogen bond (GLN279, ARG442 and POS1), Carbon Hydrogen Bond (POS1) and Pi-doner hydrogen bond with ASP303. It also showed hydrophobic interactions, Pi-Pi Stacked and Pi-Alkyl with PHE303 and POS1 respectively. Second hit Simalin B, binds with the α-glucosidase binding complex through conventional hydrogen bond (ASP215, GLU411, ARG442 and POS2), Carbon Hydrogen Bond ARG315 and POS2. It also showed hydrophobic interactions Alkyl (POS2), and Pi alkyl (TYR72, TYR158, PHE314, TYR316, HIS351 and POS2).

Linarin being third potent hit, binds with the α-glucosidase binding complex through conventional hydrogen bond (THR306, ARG315, and POS4), Carbon Hydrogen Bond (PHE314 and POS4). It also showed electrostatic interaction (Pi-anion) with GLU277 and hydrophobic interactions, Pi-Pi S and Pi-Alkyl with PHE303 and TYR72, TYR158, PHE178, POS4 respectively. The interaction detail between the nine selected compounds (Pelargonin, Simalin B, Linarin, Rutin, Nicotiflorin, Simalin A, Mangiferin, quercetin and apigenin) and amino acids residue at the substrate binding site of α-glucosidase are presented in Table 3.

3.3. Physicochemical properties of potent hits via computational analysis

Hit compounds were selected on the base of their lowest docking score values and significant binding interactions with α-glucosidase. The top hits were chosen for further evaluation of their physicochemical properties and drug-likeness. The radar plot depicted in Fig. 3 provides a clear indication that the hit compounds possess suitable physicochemical properties for oral provision. While some compounds deviated slightly from the rules, as shown in Table 4, all these phytochemicals obey Pfizer rule's requirements. According to this rule, the molecular weight (MW) should be in range of 100 ~ 600 g/mol, the logarithm of the partition coefficient (MlogP) should be < 5, the hydrogen bond acceptors number (nHA) should be < 10, and the number of hydrogen

Table 2
MolDock score of top hit compounds at the binding sites of α-glucosidase.

Alpha-glucosidase binding activity			
Compounds	**PubChem CID**	**MolDock Score**	**HBond**
Pelargonin	441,772	−174.28	−22.81
Simalin B	102,217,963	−161.08	−10.41
Linarin	5,317,025	−146.68	−16.15
Rutin	5,280,805	−142.24	−16.56
Nicotiflorin	5,318,767	−134.14	−12.29
Simalin A	102,217,962	−125.94	−15.39
Mangiferin	5,281,647	−110.57	−9.42
Quercetin	5,280,343	−102.50	−10.98
Apigenin	5,280,443	−102.45	−8.57
Acarbose	41,774	−107.89	−16.98

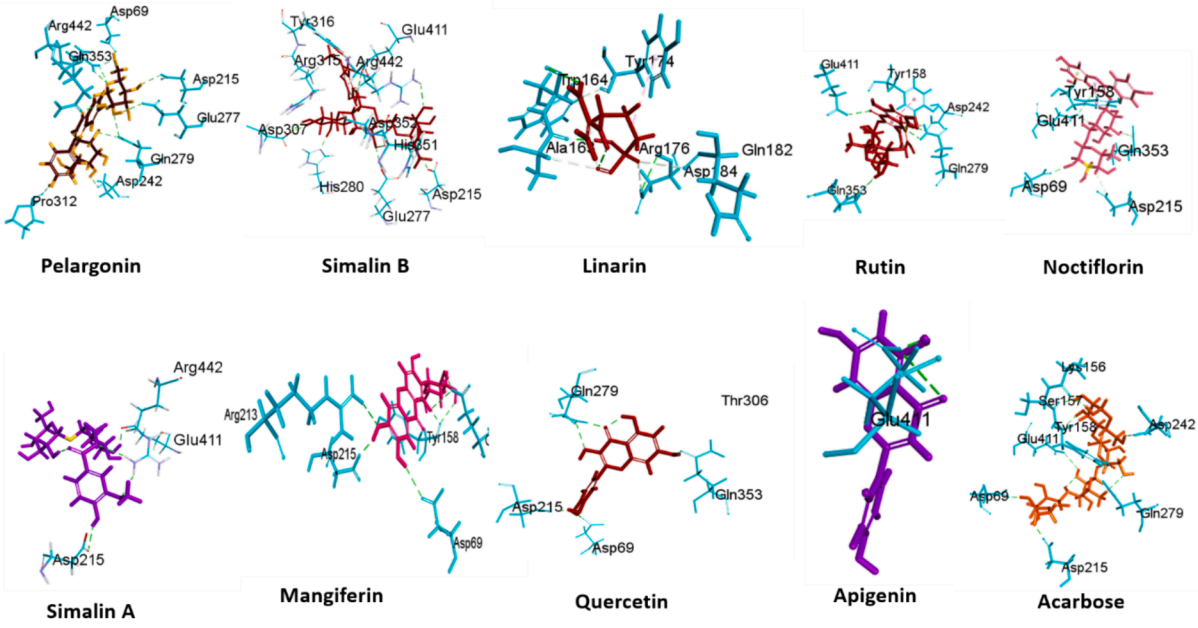

Fig. 2. Three-dimensional representation depicting the selected docked complex with maltase-glucoamylase, an α-glucosidase enzyme.

Table 3
The amino acids and the types of interactions involved in the binding with α-glucosidase.

Pelargonin				Simalin B				Linarin				Rutin			
T	**C**	**Interacting residues**	**D**	**T**	**C**	**Interacting residues**	**D**	**T**	**C**	**Interacting residues**	**D**	**T**	**C**	**Interacting residues**	**D**
Hydrogen Bond	**Conventional Hydrogen Bond**	GLN279	2.62	**Hydrogen Bond**	**Conventional Hydrogen Bond**	ASP215:OD1	2.65	**Hydrogen Bond**	**Conventional Hydrogen Bond**	THR306:HG1	2.51	**Hydrogen Bond**	**Co. HB**	GLN279	2.43
		GLN279	2.80			GLU411:OE2	2.55			ARG315:HN	1.74			GLN279	2.39
		ARG442	2.33			ARG442: HH21	2.36			POS4:H17	2.35			POS5	1.72
		ARG442	1.84			POS2:H20	2.26			POS4:H18	1.63			POS5	1.51
		ARG442	2.23			POS2:H20	2.87			POS4:H19	2.16			POS5	2.32
		POS1	2.09			POS2:H24	1.81			POS4:H20	2.37			POS5	2.13
		POS1	2.43			POS2:H25	1.67			POS4:H21	2.70			POS5	2.13
		POS1	2.41			POS2:H26	1.66			POS4:H25	1.59		**Ca. HB**	POS5:H6	2.87
		POS1	2.43			POS2:H27	2.03			POS4:H25	2.15			POS5:H8	2.80
		POS1	1.71			POS2:H28	2.42		**Ca. HB**	PHE314	2.51			POS5:H10	2.48
		POS1	2.33			POS2:H29	1.63			POS4	1.39			POS5:H11	2.78
	Ca. HB	POS1:H2	2.77		**Ca. HB**	ARG315:HD1	2.69			POS4	2.96	**H**	**Pi -S**	POS5:H5	2.45
		POS1:H3	2.29			POS2:H5	1.62			POS4	2.75		**Alkyl**	POS5:C12	4.16
		POS1:H10	2.28			POS2:H14	2.43	**E**	**Pi- Anion**	GLU277	3.81		**Pi-Pi T-shaped**	TYR158	4.19
		POS1:H14	3.06			POS2:H15	2.63				PHE178	5.06			
	Pi-D HB	ASP307	3.51			POS2:H16	2.76								
H	**Pi-Pi S**	PHE303	5.27			POS2:H18	2.97								
		PHE303	4.44			POS2:H40	2.41	**H**	**Pi-Pi S**	PHE303	4.07	**E**	**Pi-Cation**	ARG442:NH1	3.49
	Pi-Alkyl	POS1	4.59	**H**	**Alkyl**	POS2:C25	3.65			PHE303	4.57		**Pi-Anion**	GLU277:OE2	4.61
				POS2:C26	4.39		**Pi-Alkyl**	TYR72	5.14			ASP352: OD1	4.75		
			Pi-Alkyl	TYR72	3.32			TYR158	3.80			GLU411: OE2	4.83		
				TYR158	3.70			PHE178	4.18						
				PHE314	3.81			POS4	5.05	**H**	**Pi-Pi T-shaped**	TYR72	5.74		
				TYR316	4.11										
				HIS351	4.35										
				POS2	4.85										

Nicotiflorin				Simalin A				Mangiferin				Quercetin			
T	**C**	**Interacting residues**	**D**	**T**	**C**	**Interacting residues**	**D**	**T**	**C**	**Interacting residues**	**D**	**T**	**C**	**Interacting residues**	**D**
Hydrogen Bond	**Co. HB**	ARG442: HH12	2.54	**Hydrogen Bond**	**Conventional Hydrogen Bond**	GLN279: HE22	1.76	**Hydrogen Bond**	**Conventional Hydrogen Bond**	ARG213: HH21	2.41	**Hydrogen Bond**	**Conventional Hydrogen Bond**	GLN279: HE21	2.66
		POS6:H17	2.67			ARG442: HH11	2.50			GLU411:OE2	3.35			GLN279: HE22	1.88
		POS6:H19	1.75			ARG442: HH12	2.59			POS3:H8	1.68			ARG315:HE	2.20
		POS6:H21	1.88			POS4:H15	1.84			POS3:H9	2.66			ARG442: HH12	2.62
		POS6:H29	2.30			POS4:H16	1.91			POS3:H13	1.94			POS2:H7	1.79
	Ca. HB	ARG315:HD2	2.39			POS4:H17	2.44			POS3:H17	2.76			POS2:H8	2.15
		POS6:H1	2.53			POS4:H25	2.24			POS3:H18	1.70			POS2:H9	1.65
		POS6:H8	2.67		**Ca. HB**	POS4:H2	2.37		**Ca. HB**	ARG315:HD1	2.29			POS2:*H*10	1.60
		POS6:H9	1.97			POS4:H6	1.48			POS3:H1	2.45	**H**	**Pi-Pi T-shaped**	TYR72	5.74
	Pi-Lone Pair	TYR158:O	2.91			POS4:H9	1.86			POS3:H1	2.81	**E**	**Pi-Cation**	ARG442:NH1	3.49
Others	**Pi-Pi S**	TYR158	5.35			POS4:H27	2.51			POS3:H4	2.18		**Pi- Anion**	GLU277:OE2	4.61
H	**Pi-Alkyl**	PHE178	4.88		**Pi-D HB**	GLU277:OE2	3.78	**H**	**Pi-Pi T-shaped**	TYR158	5.44			ASP352:OD1	4.75

(*continued on next page*)

Table 3 (*continued*)

Pelargonin				Simalin B				Linarin				Rutin			
T	**C**	**Interacting residues**	**D**	**T**	**C**	**Interacting residues**	**D**	**T**	**C**	**Interacting residues**	**D**	**T**	**C**	**Interacting residues**	**D**
		POS6	5.11	**H**	Pi-Pi Stacked	PHE178	5.07			TYR158	5.02			GLU411:OE2	4.83
		Pi-Alkyl	TYR72	3.54		**Pi-Alkyl**	POS3	5.46							
			HIS351	4.73											
			POS4	4.99											

Apigenin				Acarbose			
T	**C**	**Interacting residues**	**D**	**T**	**C**	**Interacting residues**	**D**
Hydrogen Bond	**Conventional Hydrogen Bond**	ARG442:HH12	2.52	**Hydrogen Bond**	**Conventional Hydrogen Bond**	GLN279:HE22	2.59
		POS3:H8	1.99			POS1:*H*11	2.25
		POS3:H9	1.87			POS1:H26	2.50
	Ca. HB	ARG315:HD2	2.39			POS1:H28	2.84
E	**Pi-Cation**	ARG442:NH1	1.82			POS1:H37	2.21
H	**Pi-Pi S**	PHE178	3.94			POS1:H38	1.58
	Pi-Pi T-shaped	TYR72	5.68			POS1:H39	1.66
	Pi-Alkyl	POS3	5.07			POS1:H40	1.68
			POS1:H41	2.17			
			POS1:H42	2.15			
			POS1:H43	1.69			
		Ca. HB	POS1:H1	2.38			
			POS1:H8	1.61			
			POS1:H9	2.58			
			POS1:H15	2.33			
			POS1:H16	2.82			
			POS1:H23	2.99			
			POS1:H35	2.00			
		Pi-D HB	POS1:H36	2.46			
	H	**Pi −S**	POS1:H17	2.68			

Here, T represent Types, C represents Category, D represents Distance (Å), H = Hydrophobic interactions E represents Electrostatic interactions, Pi-S: Pi Sigma, Pi-Pi S represents Pi-Pi Stacked, Pi-A = Pi-Alkyl, Pi-DHB = Pi-Donor Hydrogen Bond, Ca.HB = Carbon Hydrogen Bond, Pi-C = Pi-Cation

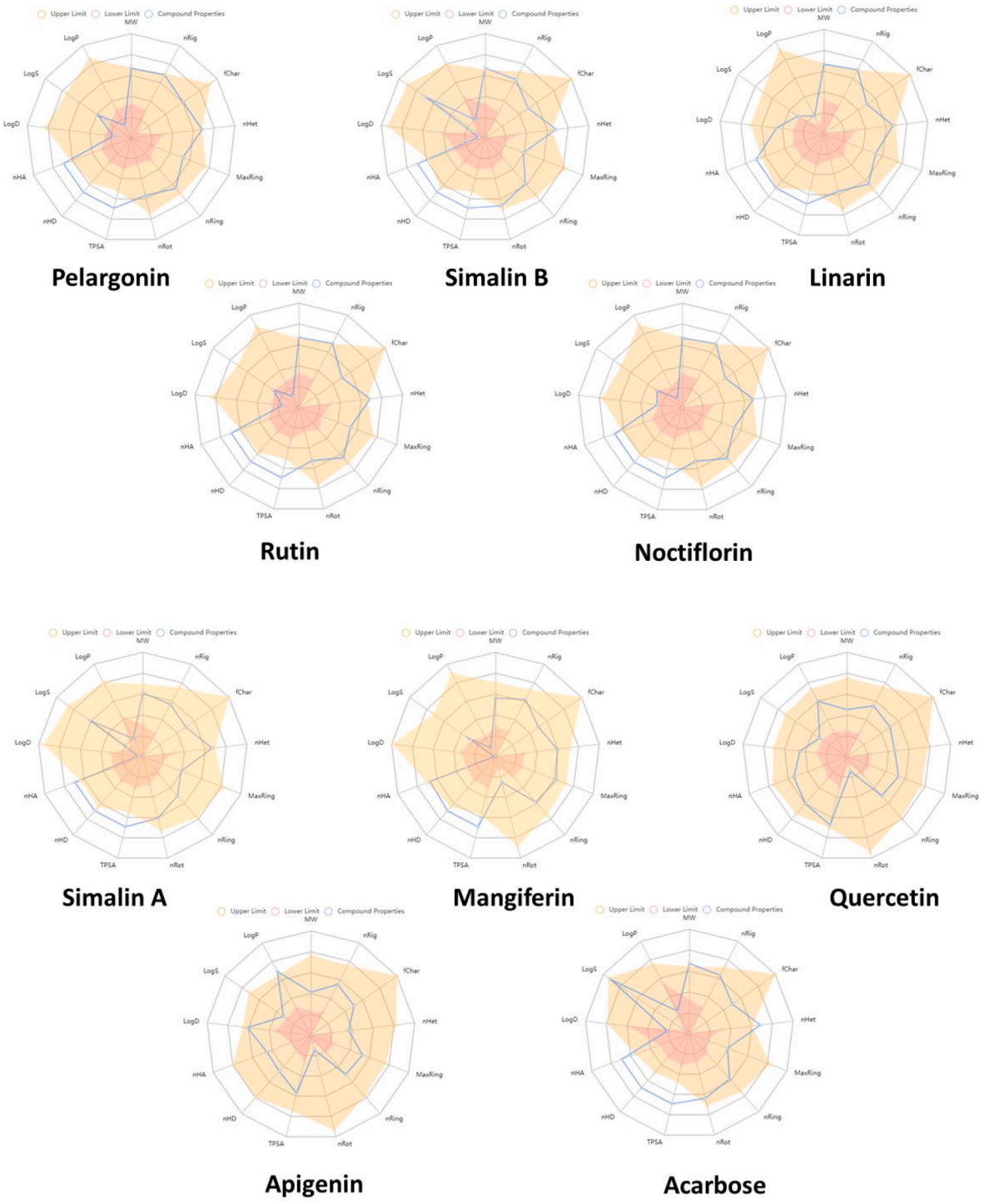

Fig. 3. Showing the physicochemical properties of potent hits in radar plot. Brown area represents the upper limit, the blue area represents the compound's property, and the pink area represents the lower limit of the physicochemical property.

bond donors should be in range of 0 ~ 7. Furthermore, these compounds demonstrated drug-like properties in terms of medicinal chemistry characteristics, as they complied with the drug rules of Pfizer criteria. This suggests that these phytochemicals have the potential to serve as viable drug candidates.

3.4. *ADMET profiling of hit compounds*

We proceeded to carry out ADMET profiling (Absorption, Distribution, Metabolism, Excretion and Toxicity) study for the nine selected compounds against alpha glucosidase using ADMET lab 2.0 online platform. The ADMET profiling of compounds are presented in Table 5. Accurate ADMET profiling plays important role in ensuring the safe drug delivery. All these phytochemicals cannot cross blood brain barrier (BBB) except Simalin A and also do not cause any cardiovascular toxicity (hERG) and Skin irritation. Among all these active compounds Apigenin and Quercetin showed high gastrointestinal absorption. On the other hand, Linarin, Rutin and Nicotiflorin showed positive AMES mutagenicity while Pelargonin, Simalin B, Simalin A, Apigenin did not exhibit carcinogenicity and safer α-glucosidase inhibitors. In the context of

Table 4
Physicochemical properties of potent hits.

Physicochemical properties	Optimal	Pelargonin	Simalin B	Linarin	Rutin	Nicotiflorin	Simalin A	Mangiferin	Quercetin	Apigenin	Acarbose
Molecular Weight (MW)	100 ~ 600	595.17	624.23	592.18	610.15	594.16	492.15	422.08	302.040	270.050	645.250
nHA	0 ~ 12	15	17	14	16	15	14	11	7	5	19
nHD	0 ~ 7	10	8	7	10	9	8	8	5	3	14
nRot	0 ~ 11	7	10	7	6	6	8	2	1	1	9
nRing	0 ~ 6	5	4	5	5	5	3	4	3	3	4
MaxRing	0 ~ 18	10	6	10	10	10	6	14	10	10	6
nHet	1 ~ 15	15	17	14	16	15	14	11	7	5	19
nRig	0 ~ 30	29	24	30	30	30	19	23	18	18	24
TPSA	0 ~ 140	250.52	244.91	217.97	269.43	249.2	225.06	201.28	131.360	90.900	321.170
logS	−4 ~ 0.5	−2.732	−0.687	−3.890	−3.928	−3.952	−1.085	−3.626	−3.671	−3.606	0.377
logP	<5	−0.921	−2.046	0.386	−0.763	−0.553	−1.977	−0.521	2.155	3.307	−4.370
logD	1 ~ 3	0.748	−0.283	1.792	0.695	1.052	0.181	0.039	1.767	2.704	−2.523
Medicinal chemistry	Pfizer Rule	Accepted	Accepted	Accepted	Accepted	Accepted	Accepted	Accepted	Accepted	Accepted	Accepted

Table 5
ADMET profiling of top hits.

Category	Property	Pelargonin	Simalin B	Linarin	Rutin	Nicotiflorin	Simalin A	Mangiferin	Quercetin	Apigenin	Acarbose
Absorption	Caco-2> −5.15	−6.4/Low	−6.3/ Low	−6.0/ Low	−6.3/ Low	−6.2/Low	−6.3/ Low	−6.2/ Low	−5.2/High	−4.8/High	−6.1/ Low
	PgN-Inhibitor	−−−	−−−	−−−	−−−	−−−	−−−	−−−	−−−	−−−	−−−
	PgN-Substrate	+++	+++	+++	+++	+++	+++	+	−−−	++	++
	HIA	+++	+++	+++	+++	−−−	+++	+++	−−−	−−−	+++
Distribution	PPB	73.8 %	23.9 %	71.1 %	83.8 %	83.48 %	26.05 %	84.9 %	95.4 %	97.2 %	8.2 %
	BBB	−	−	−−	−−	−−	+	−−−	−−−	−−−	−
Metabolism	CYP2D6 Inhibitor	−−−	−−−	−−−	−−−	−−−	−−−	−−−	−	++	−−−
	CYP2D6 Substrate	−−	−−	−−	−−	−−	−−	−−	−−	++	−−−
	CYP3A4 Inhibitor	−−−	−−−	−−−	−−−	−−−	−−−	−−−	−	++	−−−
	CYP3A4 Substrate	−−−	−−−	−−−	−−−	−−−	−−−	−−−	−−−	−−	−−−
	CYP2C9 Inhibitor	−−−	−−−	−−−	−−−	−−−	−−−	−−−	+	+	−−−
	CYP2C9 Substrate	−−	−−−	−	−−	+	−	−−	+	+++	−−−
	CYP2C19 inhibitor	−−−	−−−	−−−	−−−	−−−	−−−	−−−	−−−	+	−−−
	CYP1A2 Inhibitor	−−−	−−−	−−−	−−−	−−−	−−−	−−−	+++	+++	−−−
	CYP1A2 Substrate	−−−	−−	−−−	−−−	−−−	−−−	−−−	−−	−−	−−−
	CYP2C19 Substrate	−−−	+	−−	−−−	−−−	−−−	−−−	−−−	−−−	−−−
Excretion	Clearance	1.4/ Low	0.99/ Low	1.2/ Low	1.3/ Low	1.21/ Low	1.4/ Low	3.17/ Low	8.2/ Moderate	7.0/ Moderate	0.37/ Low
Toxicity	hERG	−−−	−−−	−−−	−−−	−−−	−−−	−−−	−−−	−−−	−−−
	DILI	+++	−−	+++	+++	++	+	+++	+++	++	+++
	H-HT	−−−	−−−	−−−	−−−	−−−	−−−	−−	−−−	−−−	−−
	FDAMDD	−−−	−−−	−−−	−−−	−−−	−−−	−−−	−	−	−−−
	Ames	−	−−	++	++	+++	−−	++	+	−	−−−

classification endpoints, the prediction probabilities undergo a transformation into six distinct symbols to facilitate interpretation. The probability range of 0–0.1 is denoted by '—', while the interval of 0.1–0.3 is represented as '–'. Similarly, the range 0.3–0.5 is symbolized by '-', and 0.5–0.7 is expressed as '+'. Moving towards higher probabilities, the interval 0.7–0.9 is indicated by '++', and finally, the range 0.9–1.0 is conveyed through the symbol '+++'. This categorization system offers a concise and standardized representation of prediction confidence levels across different probability thresholds.

3.5. *In vitro α-Glucosidase inhibition assay for bioactive compounds*

Commercially available phytochemicals were further tested against α-glucosidase to validate our *in silico* results. For this purposes Apigenin, Quercetin and Mangiferin were used against α-glucosidase to determine their inhibitory activity. The inhibitory effect of the Apigenin, Quercetin and Mangiferin was compared with *B. ceiba* extract. *B. ceiba* showed IC_{50} at a concentration of 1.95 ± 0.29 μg/mL, on the other hand Apigenin, Quercetin and Mangiferin showed higher inhibition against α-glucosidase with IC_{50} values at a lower concentration of 0.83 ± 0.07 μg/mL, 0.96 ± 0.01 μg/mL and 1.47 ± 0.16 μg/mL respectively Fig. 4.

4. Discussion

Plants and their derived compounds have long been used as a valuable source of medicines for the treatment of diseases. In particular,

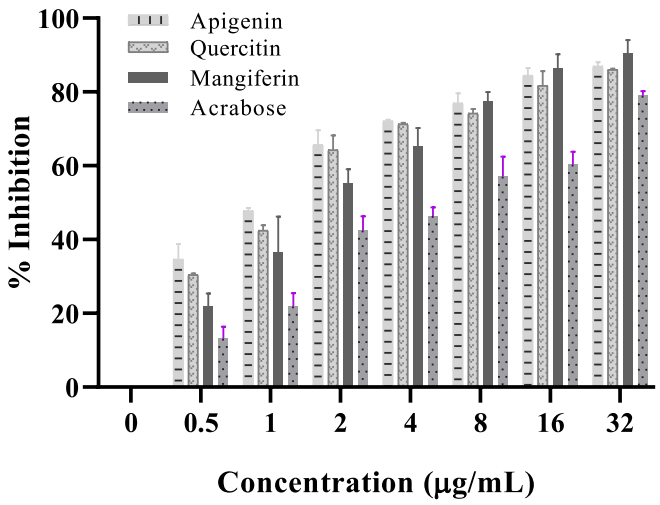

Fig. 4. α-Glucosidase inhibition (%age) by increasing concentrations of Apigenin, Quercetin and Mangiferin as compared to acarbose. The resulting IC_{50} values are 0.83 ± 0.07 µg/mL for Apigenin, 0.96 ± 0.01 µg/mL for Quercetin and 1.47 ± 0.16 µg/mL for Mangiferin. The experiment was repeated in triplicates (n = 3) mean values ± Standard deviation.

plant-based anti-diabetic medications have been widely utilized since ancient times due to their affordability and safety as compared to synthetic drugs. (Alam et al., 2022). In this study we screened 51 extracts of different parts of 35 plants against α-glucosidase. Glucosidases catalyze dietary carbohydrates from the small intestine and facilitate their absorption, specifically their glucose contents (Ahamad et al., 2011). From this screening, *B. ceiba* was found highly potent inhibitor of α-glucosidase. Different studies have shown that *B. ceiba* bark is a chief source of flavonoids, as compared to phenolic compounds where Apigenin and Quercetin are common flavonoids in *B. ceiba* extract and have anti-diabetic potential due to intestinal α-glucosidases inhibition (Vaghasiya et al., 2011, Hassan, 2018, Depani et al., 2019). PNPG substrate was used to investigate the inhibitory potential of *B. ceiba* against α-glucosidase. Similar results also reported by Hung et al.,2019 that, the isolated compounds from Root extract of *Bombax malabarica* showed alpha glucosidease activity of shorealactone with IC_{50} values 224 µM, l-epicatechin 5-O-β-D-xyloside with IC_{50} values 345 µM, and 2-C-[β-D-apiosyl-(1 → 6)]- β-D-glucosyl]-1,3,6-trihydroxy-7-methoxyxanthone with IC_{50} values 285 µM (Lam et al., 2019).

Inhibitory concentration (IC_{50}) was 1.95 ± 0.29 µg/mL in *B. ceiba*, represent higher inhibition than already reported α-glucosidase inhibitor acarbose (IC_{50}: 3.14 ± 0.49 µg/mL). There are different plants such as *Allium sativum* (Eidi et al., 2006), *Gymnema sylvestre* (Spasov et al., 2008), *Citrullus colocynthis* (Gurudeeban and Ramanathan, 2010), *Trigonella foenum greacum* (Renuka et al., 2009), *Momordica charantia* (Chaturvedi, 2012), *Ficus bengalensis* (Gayathri and Kannabiran, 2008), *Syzygium cumini* (Kumar et al., 2008) etc. already have been reported showing better antidiabetic potential than commercially available medicines. The demand for novel drugs with enhanced effectiveness and reduced toxicity remains persistent. The drug discovery and development procedure is highly expensive and time killing. In addition to the obstacles encountered during target validation and hit identification, clinical trials frequently show a significant failure rate due to factors such as insufficient pharmacokinetics, limited efficacy, and high toxicity (Chang et al., 2023). The field of drug design has experienced a significant transformation with the introduction of *in silico* analysis, which has led to improved efficiency and cost reduction compared to traditional drug design methods. The integration of advanced databases, software, and tools in bioinformatics has played a crucial role in the exploration and dissemination of numerous novel therapies and applications (Musuamba et al., 2021). In this study, a collection of phytocompounds obtained from PubChem IDs was subjected to docking simulations with α-glucosidase to assess their potential as α-glucosidase inhibitors. Out of these compounds nine compounds were selected as α-glucosidase inhibitors by their minimum energy and top MolDock scores. Recent investigations have highlighted the potential interactions of these bioactive phytochemicals and their significant hydrophobic contact with α-glucosidase. The docking analysis revealed binding energies of Pelargonin, Simalin B, Linarin, Rutin, Nicotiflorin, Simalin A, Mangiferin, Quercetin, Apigenin at the α-glucosidase cavity scored were found to be −174.28 Å, −161.08 Å, −146.68 Å, −142.24 Å, −134.14 Å, 125.94 Å, 110.57 Å, −102.5 Å, and −102.45 Å respectively, along with the formation of several hydrogen bonds. These compounds exhibited binding interactions with residues such as HIS112, ASP69, ARG442, GLU277, and ARG213 of α-glucosidase, consistent with previous studies highlighting their strong inhibitory activity and binding capabilities of with α-glucosidase (Yan et al., 2014). Additionally, a comprehensive evaluation of these compounds based on the "Rule of Five" (Ro5) was conducted to check their drug-likeness and molecular properties (Chen et al., 2020). Advanced high-performance ADMET profiling analyses have emerged as valuable tools in early-stage drug discovery, facilitating the identification of active lead compounds (Ferreira and Andricopulo, 2019). The ADMET compound profiling conducted in this study confirmed the favorable absorption properties of all the compounds, without producing any adverse effects. Various models assessing P-glycoprotein substrates, blood–brain barrier (BBB) penetration, and gastrointestinal uptake were employed to evaluate the ADMET-related characteristics of these potential compounds. Notably, all these phytochemicals showed significant gastrointestinal absorption while showing limited BBB penetration except Simalin A, suggesting a reduced risk of harmful or adverse side effects compared to acarbose. It was observed that all these phytochemicals exhibited susceptibility with P-gp substrate except Quercetin. P-glycoproteins play a crucial role in transporting drugs to targeted organs (Elmeliegy et al., 2020). Furthermore, Apigenin and Quercetin exhibited positive inhibition against CYP1A2 and CYP2C9, indicating the potential for drug-drug interactions with these enzymes. Importantly, these phytochemicals didn't exhibit toxicity, such as skin sensitization, mutagenesis and cardiotoxicity as non-inhibitors of hERG (Priest et al., 2008). Among potent compounds, commercially available phytochemicals, Apigenin, Quercetin, and Mangiferin, also accessed by *in vitro* enzyme inhibitory assay to validate *in silico* results. these compounds exhibited significant inhibitory activity with the IC_{50} values 0.83 ± 0.07 µg/mL, 0.96 ± 0.01 µg/mL, and 1.47 ± 0.16 µg/mL respectively, which were notably less than acarbose. Li et al., (2009) also reported Quercetin and Rutin, that these compounds showed higher anti-diabetic results than acarbose (Li et al., 2009). There are chemically prepared inhibitors already reported with strong α-glucosidase inhibitory activity than standard drug (Rashid et al., 2022). Many α-glucosidase inhibitors have shown efficacy at lower concentrations (IC_{50}) compared to the positive control, indicating their potential therapeutic value (Yin et al., 2014). Previous studies have reported similar findings in *Aegles marmelos* and *Syzygium cumini*, where they demonstrated the ability to inhibit α-glucosidase and GLUT4 expression in adipocytes and contribute significantly to regulating blood glucose levels in individuals with diabetes (Anandharajan et al., 2006). In light of potential side effects and the higher costs associated with synthetic compounds, there is a preference for natural bioactive substances as potential candidates for drug development (Nisbet and Moore, 1997, Nisar et al., 2018). These findings could be useful for the development of novel therapeutic approaches by *B. ceiba* and its active metabolites for managing diabetic hyperglycemia via targeting α-glucosidase. Although two compounds Simalin A and B reported very first time in this study as α-glucosidase modulators yet their biochemical and *in vitro* evaluation is strongly recommended for their validation as α-glucosidase inhibitors.

5. Conclusion

In this study, *in vitro* enzymatic assay screening of 51 plant extracts was performed. The screening results showed that *B. ceiba* bark extract exhibited strong α-glucosidase inhibition with IC_{50} value 1.95 ± 0.29 μg/mL. To the best of our knowledge, this is first report discloses *Bombax ceiba* as potent α-glucosidase inhibitor. Literature based library of 78 phytochemicals of *B. ceiba* was prepared and these compounds were docked with α-glucosidase binding site. Based on the *in silico* data, nine potent hits were identified with best binding affinities and showed favorable ADMET properties. Among these, Simalin A and B were identified as α-glucosidase modulators through virtual screening for the first time. Although, their in-vitro and biochemicals studies are strongly recommended to ensure α-glucosidase as the prime molecular target of these compounds. Furthermore, commercially available three phytochemicals, Apigenin, Quercetin and Mangiferin, were validated as α-glucosidase inhibitors using *in vitro* enzymatic assay with IC50 value 0.83 ± 0.07 μg/mL, 0.96 ± 0.01 μg/mL, 1.47 ± 0.16 μg/mL respectively. On the base of these findings, it is suggested that *B. ceiba* bark extract and its metabolites may holds the potential as a natural resource for managing hyperglycemic conditions in diabetic patients via targeting α-glucosidase. As α-glucosidase is a rate-limiting enzyme of intestinal carbohydrate digestion; therefore, it is recommended to evaluate the inhibitory efficacy of these compounds on the other key proteins involved in intestinal carbohydrate digestion. Additionally *in vivo* studies are recommended to validate their effectiveness and safety. Subsequently, clinical trials should be conducted to evaluate their potential as antidiabetic agents in diabetic patients.

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CRediT authorship contribution statement

Mudassir Hassan: Conceptualization, Software, Validation, Writing – original draft, Writing – review & editing. **Azhar Rasul:** Conceptualization, Supervision, Writing – review & editing. **Farhat Jabeen:** Investigation, Writing – review & editing. **Salma Sultana:** Formal analysis, Writing – review & editing. **Maria Manan:** Methodology, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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