MOLECULAR DOCKING BASED ANTIDIABETIC SCREENING OF *CURCUMA CAESIA* ROXB.

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ABSTRACT

High blood glucose levels are a long-term metabolic condition known as diabetes mellitus (DM). In most cases, the hyperglycemic syndrome causes vascular damage and chronic nerve loss.Type 2 diabetes is the most prevalent and has spread over the entire planet. Controlling levels of blood glucose has remained a contentious problem for sufferer despite the development of numerous treatment strategies to control type 2 DM. The majority of prescription medications can have a variety of adverse effects, including gastrointestinal issues. So there is a significant demand for the creation of noval, effective anti-diabetic medicine with fewer side issues.In this study, different computational tools were used, including molecular docking and ADME tests of components of *Curcuma caesia* against alpha-amylase, alpha-glucosidase, and dipeptidase receptor. According to molecular docking studies, the alpha-amylase receptor binding pocket of the targeted drug (PDB ID: 4GQR) for coniferol, bisdemethoxycurcumin, desmethoxycurcumin, and curcumin all shown good docking scores.The selected (PDB ID: 6C9X) for alpha-glucosidase receptor compound Xanthinin, Dibutyl phthalate, Desmethoxycurcumin, and Aconerol showed good docking scores within binding pockets. The molecules Ivalin, Dibutyl phthalate, Terpinen-4-ol, and Arglabin showed a superior docking scores within the binding pocket of the chosen (PDB ID: 1ITU) for dipeptidase receptor, and these substances can be employed as lead molecules for rational drug advancement. According to ADME research, the substances Aconerol, Arglabin, Bisdemethoxycurcumin, Coniferol, Curcumin, Desmethoxycurcumin, Dibutylphthalate, Ivalin, Terpinen-4-ol, and Xanthinin fall under the parameters of the five rule of Lipinski. The research revealed that the constituents (Aconerol, Arglabin, Bisdemethoxycurcumin, Coniferol, Curcumin, Desmethoxycurcumin, Dibutyl phthalate, Ivalin, Terpinen-4-ol, and Xanthinin) respond to Lipinski's rule, making them suitable lead molecules for more research.

Keywords: ADME, ant-diabetic activity, *Curcuma caesia*, curcumin, molecular docking.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic condition characterised by persistent increases in blood sugar levels, high serum triglycerides, polyuria, polyphagia, and polydipsia [1, 2]. Elevated blood glucose levels, which are a symptom of type 2 diabetes mellitus (T2DM), are a dangerous, long-term metabolic illness brought by insufficient insulin production or insulin resistance [3]. 463 million persons (20-79 years) in India were estimated with DM, and by 2045, that figure is expected to rise to 700 million [4] according to estimates from the International Diabetes Federation (IDF). According to data from 2019, there are 87.9 million people with DM living in the South East Asia Region, the disease's epicentre, of which 34.3 percent reside in cities and 49.4 percent in rural regions[5]. In middle-income South Asian nations, the vast majority of people (99.2%) have DM. A frequency of 8.7% in the adult population has been estimated for Sri Lanka, a developing country in South Asia (20 -79 age) [5].Due of DM's long-duration effects, it has become one of the major global reasons of morbidity [6].Based on the pathophysiology, diabetes can be categorised as insulin-dependent (type I), non-insulin-dependent (type II), or gestational.

The body's insulin receptors become resistant to the typical actions of insulin in Type 2 DM, which is more frequent than the other forms.In order to control the situation, the pancreas then generates more insulin in response to the increased blood glucose levels. However, excessive insulin synthesis causes cells to become exhausted [7, 8].

As a result of chronic hyperglycemia, patients with DM may develop problems like retinopathy, cataracts, neuropathy, peripheral vascular insufficiencies, nephropathy, and damaged nerves [8–10]. For stopping the spread of the disease, various mechanisms and pathways are taken into account.They could include inhibiting intestinal alpha-glucosidase and amylase, insulin synthesis and secretion, protecting against oxidative stress, inhibiting the formation of advanced glycation end products, reduction of plasma glucose levels, alteration of hexokinase and glucose-6-phosphate enzyme activity, inhibiting postprandial hyperglycemia, stimulating GLUT-4, reduction of G6P activity [11, 8].

The inhibition of important enzymes is one of the most widely used methods for controlling blood glucose levels [12]. Two carbohydrate digestion enzymes, α-glucosidase and α-amylase, can enhance postprandial hyperglycemia (PPHG). As a result, their inhibition is crucial for managing PPHG in individuals with type 2 diabetes. While α-amylase inhibition prevents the conversion of starch to glucose, inhibition of α-glucosidase reduces the hydrolysis of disaccharides.In studies where these substances have been used, patients' blood glucose levels have been decreased [13, 14]. The most significant side effect of the FDA-approved type 2 DM medications, such as voglibose, sulphonylureas, acarbose, thiazolidine, and miglitol, is gastrointestinal distress, which requires further treatment. Investigation of various treatment options with fewer adverse effects is highly desired in the US [15–17].

Important enzymes that impact the breakdown and absorption of starch and other carbohydrates in the diet are alpha-amylase and alpha-glucosidase [18]. Dextrin and oligosaccharides are produced from starch by the hydrolyzes of the alpha -D-1,4-glucosidic link by alpha-amylase, and glucose is produced from dextrin and oligosaccharides by alpha-glucosidase [19, 18]. The subsequent transfer of glucose to blood arteries raises postprandial blood glucose, resulting in obesity or diabetes [20, 21]. As a result, inhibiting alpha-amylase and alpha-glucosidase activity decreases starch digestibility and postpones starch breakdown and glucose absorption [22, 23].Although acarbose and miglitol, two antihyperglycemic medications, now suppress the activities of alpha- amylase and glucosidase, certain negative side effects, such as diarrhoea, flatulence, and liver illness, can happen [24]. Because of this, polyphenols with a range of biological actions have been shown to be possible natural inhibitors of alpha-amylase and alpha-glucosidase activity [25].

The perennial herb *Curcuma caesia* Roxb., often known as Kali haldi, is widespread in the Himalaya area, and central India. Leucoderma, asthma, tumours, piles, and other conditions have all been traditionally treated using rhizome paste. Alkaloids, steroids, phenolics, and tannins are some of the bioactive compounds that provide C. caesiafor its therapeutic significance [26]. Several medicinal benefits of C. caesia have been scientifically documented, including antioxidant, larvicidal, pneumonia, antipyretic, antimicrobial, insecticidal, asthma, antihyperglycemic, haemorrhoids, menstrual problem, epilepsy, leucoderma, inflammation, etc.[27-28].The rhizomes of C. caesia are said to contain a number of bioactive compounds, including flavonoids, curcumin, 1, 8-cineole, amino acids, alkaloids, ar-turmerone, curcuminoids, and phenolics[29-30]. These bioactive compounds were have been

documented for their pharmacological effects like anti-inflammatory, antimicrobial, antioxidant, anticoagulant, antimicrobial, hypoglycaemic [31], smooth muscle relaxant [32], anti-diabetic activity [33],free-radical scavenging opposed to reactive oxygen, antitumour activity [34],anti-mutagenic activity[35], anti-mycobacterial activity [36]and antitoxicity against cyclophosphamide[37].

The development of a new drug procedure is sped up by computer-aided drug designing (CADD), which extracts prospective lead molecules from large chemical libraries [38].The pharmacokinetics of lead compounds are discovered and enhanced using CADD [39].

The most effective orientation and conformation for a protein's ligand binding are the goals of a docking study, which also aids in finding the right molecule by screening through huge databases [40]. The time and budget of drug discovery have been reduced by the use of several computer tools in drug screening and design [41]. Accurate activity prediction and precise structural modelling are the key objectives of the docking investigation. The

molecular docking technique is used to investigate drug molecule orientation to the target site, drug-receptor interaction, and binding affinity [42].

Pharmacokinetics, which is the study of how drugs are absorbed, distributed, metabolised, and excreted by humans, is defined by the Lipinski rule. Because ofto its low cost and great result, ADME modelling has drawn a significant research interest in the pharmaceutical industry [43].
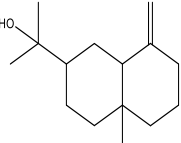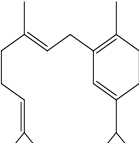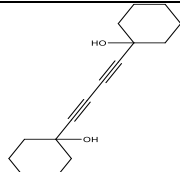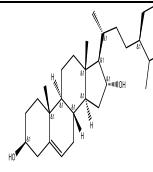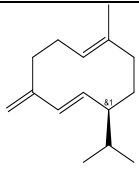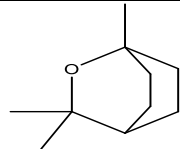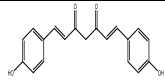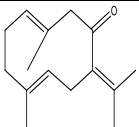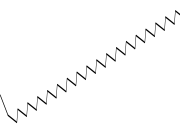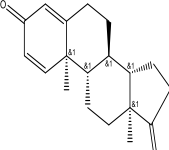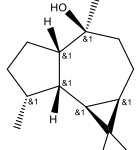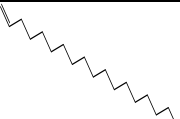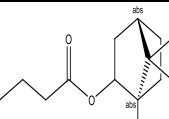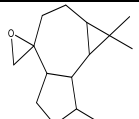
In response to the findings discussed above from the current investigation, we are reporting on the molecular docking and ADME analyses of bioactive constituents of C. caesia that were chosen from published work [44].
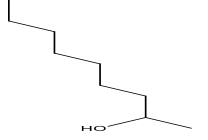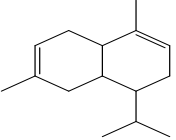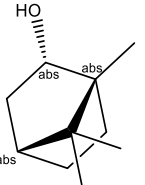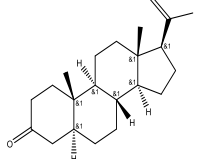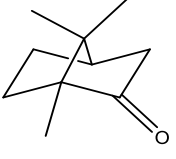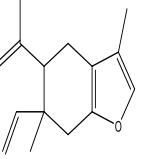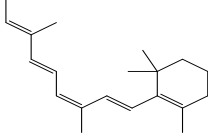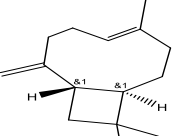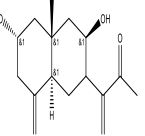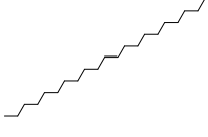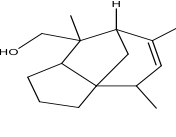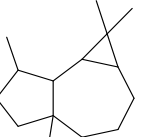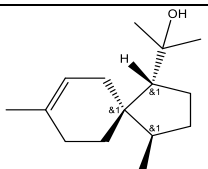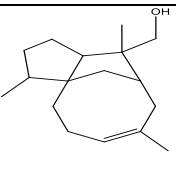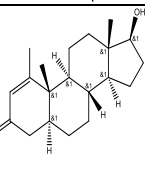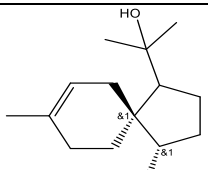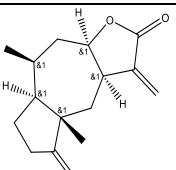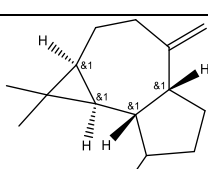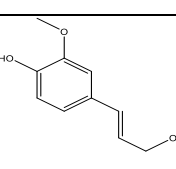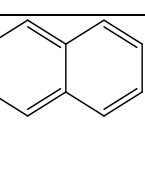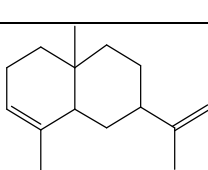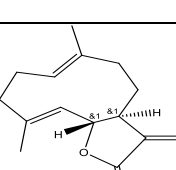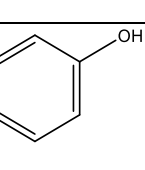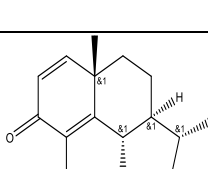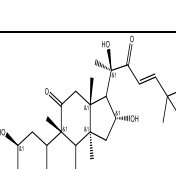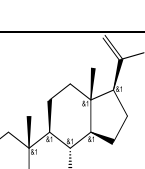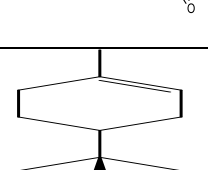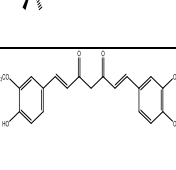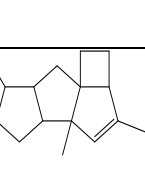
MATERIAL AND METHODS
Molecular docking study
The structures of 75 compounds of C. caesiawere selected from published work [44], sketched using ChemDraw 19.0, and are shown in Table 1. Schrodinger Suite 13.1 was used for the molecular docking
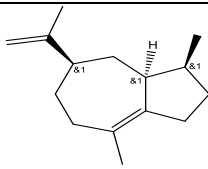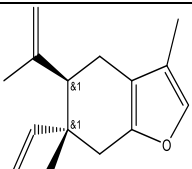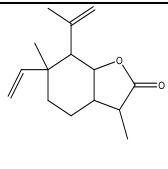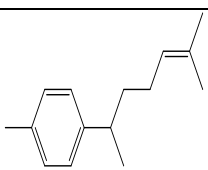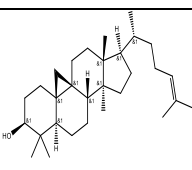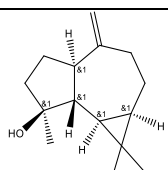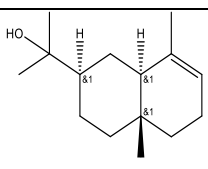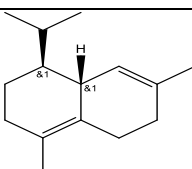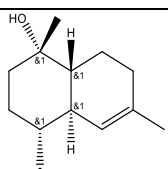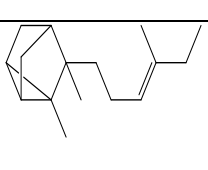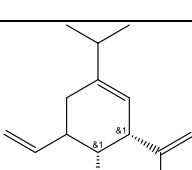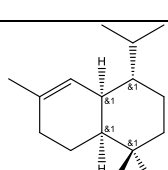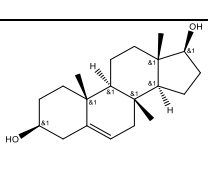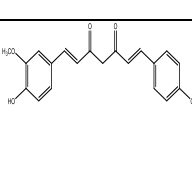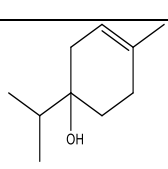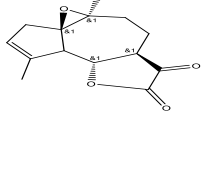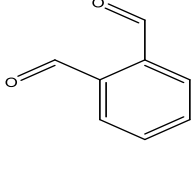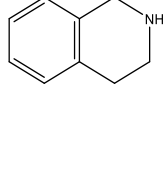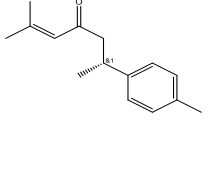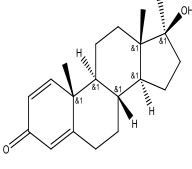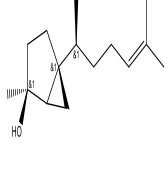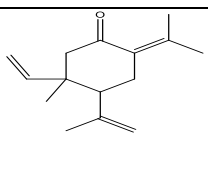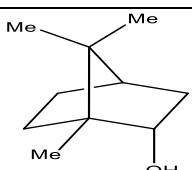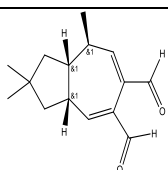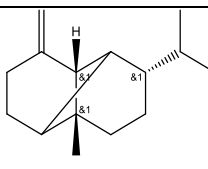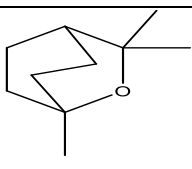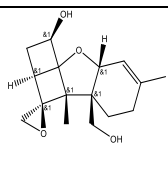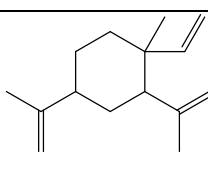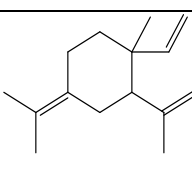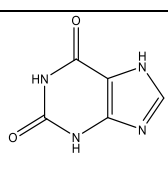
Table 1: Chemical Structure of compounds of *C. caesia* used in molecular docking

Compound Name	Chemical Structure	Compound Name	Chemical Structure	Compound Name	Chemical Structure
(+)-2-Bornanone		β-Selinenol		Geranyl-α-terpenene	
1,1'-Butadiynylene dicyclohexanol		β-Sitosterol		Germacrene D	
1,8-Cineole		Bisdemethoxycurcumin		Germacrone	
1-heptatriacotanol		Boldione		Himabaccol	
1-Nonadecene		Bornyl ester		Isoaromadendrene epoxide	

2-Nonanol		**Cadinene**		**Isoborneol**	
5 alpha-Dihydroprogesterone		**Camphor**		**Isofurano-germacrene**	
9-cis-Retinal		**Caryophyllene**		**Lvalin**	
10-heneicosene		**Cedr-8-en-13-ol**		**Ledene oxide-(1)**	
17-chloro-alpha-acorenol		**Cedren-13-ol**		**Methenolone**	
Aconerol		**Confertin**		**Methyl stearolate**	
Alloaromadendrene		**Coniferol**		**Naphthalene**	
α-Selinene		**Costunplide**		**Phenol**	
α-Santonin		**Cucurbitacin-B**		**Pregan-20-one**	
α-Terpineol		**Curcumin**		**Rotundene**	

α-Bulnesene		Curzerene		Saussurea lactone	
α-Curcumene		Cycloartanol acetate		Spathulenol	
α-Eudesmol		Delta-cadinene		τ-Cadinol	
α-Santalol		Delta-elemene		T-Muurolol	
Androstenediol		Desmethoxycurcumin		Rerpinen-4-ol	
Arglabin		Dibutyl phthalate		Tetrahydroisoquinoline	
Ar-tumerone		Dimethanodrostanolone		trans-Sesquisabinene hydrate	
β-Elemenone		Endo-Borneol		Velleral	
β-Copaene		Eucalyptol		Verrucarol	
β-Elemene		γ-Elemene		Xanthinin	

Protein preparation

Each atom must have charge and an atom type that identifies characteristics in order for docking algorithms to function. These characteristics are absent from the protein structure from the PDB that was downloaded. To incorporate these values in addition to the atomic coordinates, we must therefore generate the protein and ligand file. The Schrodinger suite's protein preparation wizard was carried out for the preparation of protein.The RCSB Protein Data Bank's high resolution downloads of the PDB IDs: 4GQR (for amylase), 6C9X (for glucosidase), and 1ITU (for dipeptidase) were processed in advance of further research. Atoms of hydrogen were added to ensure good docking electrostatic treatment. Bond order was created after the removal of water molecules [45]. To PH 7.4, the tautomeric and protonation states were produced. To prevent steric conflicts between the atoms, the optimization of atomic charges and minimization of energy protein were performed using the OPLS4 force field [46].

Ligand preparation

For the creation of 3D ligands that must interact with proteins in order to evaluate their anticancer potential, the mol2 file format is necessary. Using the maestro module, a number of heterocyclic molecules that were picked out of the literature were created. Their 3D mol data were transformed using the.maegz file with Ligprep supported software. Using the OPLS4 force field module, all ligands were minimised [47-48].For generating and assessing ligand poses within the binding sites of receptors, docking includes a search algorithm and an energy scoring function [49].

Grid generation and molecular docking

The site map tool was used to construct the best grid for the preprocessed protein (4GQR, 6C9X, and 1ITU) around its most active site. The grid-generated receptor (the protein's active site) was combined with all of the prepared ligands after grid preparation, and docking was then performed under standard precision (SP) to produce the dock score values with the protein ligand conformational complexes that were most appropriate [48].

ADME study

Determining ADME characteristics is a crucial step because the majority of pharmaceutical substances fail in clinical trials. The likelihood and ADME characteristics of the most active components were ascertained using QikProp, GLIDE,and Schrodinger v 13.1. Schrodinger 13.1's LigPrep module was used to synthesise the ligand for the ADME study in Maestro format (.maez). Then, in order to retrieve the ADME parameters, we got to work by opening the QikPro dialogue box and inserting the ligand preparation file (.maez) for the synthesised derivatives [50].

RESULTS AND DISCUSSION

From a literature review, various series of curcumin derivatives were chosen (Table 1). Using the molecular docking programme Schrodinger v. 13.1, PDB IDs 4GQR, 6C9X, and 1ITU were used to calculate the antidiabetic compounds docking scores (Table 2) in relation to standard drug Acarbose and Glibenclamide.

Table 2: Docking rating of constituents of *C. caesia* using (PDB ID: 4GQR, 6C9X, and 1ITU)

Compound Name	Docking Score (PDB ID: 4GQR)	Docking Score (PDB ID: 6C9X)	Docking Score (PDB ID: 1ITU)	Compound Name	Docking Score (PDB ID: 4GQR)	Docking Score (PDB ID: 6C9X)	Docking Score (PDB ID: 1ITU)
(+)-2-Bornanone	-6.297	-5.707	-3.902	Cucurbitacin-B	-4.732	-3.343	-3.760
1,1'-Butadiynylene dicyclohexanol	-5.229	-6.185	-4.005	Curcumin	-7.093	-6.125	-4.533
1,8-Cineole	-5.564	-5.226	-3.969	Curzerene	-4.329	-4.736	-3.111
10-heneicosene	1.056	0.271	1.829	Cycloartanol acetate	-4.517	-4.216	-2.597
17-chloro-alpha-acorenol	-5.023	-3.662	-3.776	Delta-cadinene	-5.266	-3.668	-3.360
1-Nonadecene	2.858	1.782	2.842	Delta-elemene	-4.489	-4.372	-2.447
2-Nonanol	-2.853	-2.820	-1.986	Desmethoxycurcumin	-7.119	-5.735	-4.882
5α-Dihydroprogesterone	-5.329	-3.300	-3.708	Dibutyl phthalate	-6.253	-7.185	-5.391
9-cis-Retinal	-5.318	-3.817	-2.682	Dimethanodrostanolone	-5.630	-4.016	-4.806
Acarbose	-7.370	-6.205	-4.697	Endo-Borneol	-5.423	-5.730	-3.828

Aconerol	-4.922	-6.778	-4.635	**Eucalyptol**	-5.564	-5.226	-3.969
Alloaromadendrene	-5.392	-3.361	-3.557	**-Elemene**	-4.600	-4.717	-2.863
α – Selinene	-5.184	-3.309	-3.141	**Geranyl-alpha-terpenene**	-3.984	-4.236	-2.512
α - Santonin	-5.412	-4.308	-3.963	**Germacrene D**	-5.313	-3.388	-3.967
α - Terpineol	-5.683	-5.579	-4.532	**Germacrone**	-5.395	-3.825	-3.512
α -Bulnesene	-5.676	-3.175	-4.109	**Himabaccol**	-6.243	-5.700	-3.786
α -Curcumene	-3.371	-4.119	-2.969	**Isoaromadendrene epoxide**	-5.516	-3.288	-3.908
α -Eudesmol	-5.809	-4.575	-4.562	**Isoborneol**	-5.716	-6.406	-4.114
α -Santalol	-4.050	-3.889	-2.251	**Isofurano-germacrene**	-4.329	-4.736	-3.111
Arglabin	-6.136	-3.937	-5.305	**Ivalin**	-4.808	-4.519	-5.087
Ar-tumerone	-4.674	-4.180	-3.618	**Ledene oxide-(1)**	-4.456	-4.221	-4.791
β- Elemenone	-4.246	-4.949	-3.773	**Methenolone**	-6.808	-4.205	-4.295
β -Copaene	-4.995	-3.207	-3.315	**Methyl stearolate**	0.553	-0.048	-0.131
β -Elemene	-3.907	-2.636	-2.698	**Naphthalene**	-5.077	-5.405	-3.169
β -selinenol	-4.869	-3.550	-4.750	**Phenol**	-5.695	-6.228	-4.118
β -Sitosterol	-5.818	-4.383	-2.130	**Pregan-20-one**	-5.868	-3.208	-3.033
Bisdemethoxycurcumin	-7.293	-6.552	-4.237	**Rotundene**	-5.188	-3.907	-3.375
Boldione	-5.963	-4.020	-4.542	**Saussurea lactone**	-5.901	-4.173	-3.186
Bornyl ester	-3.580	-4.460	-2.774	**Spathulenol**	-5.591	-4.949	-4.708
Cadinene	-5.376	-3.339	-3.477	**τ- Cadinol**	-5.617	-3.867	-4.072
Camphor	-6.297	-5.707	-3.902	**T- Muurolol**	-5.588	-3.928	-4.371
Caryophyllene	-5.274	-5.743	-3.094	**Terpinen-4-ol**	-5.840	-5.700	-4.933
Cedr-8-en-13-ol	-5.804	-5.398	-3.765	**Tetrahydroisoquinoline**	-5.670	-6.600	-4.745
Cedren-13-ol	-5.939	-5.318	-3.102	**trans-Sesquisabinene hydrate**	-5.274	-4.363	-3.701
Confertin	-6.015	-4.063	-4.647	**Velleral**	-5.819	-3.971	-4.227
Coniferol	-7.367	-5.412	-4.711	**Verrucarol**	-4.206	-3.511	-3.399
Costunolide	-5.586	-3.633	-4.650	**Xanthinin**	-5.852	-8.167	-4.621

Table 3: Docking score of the most active constituents using PDB ID: 4GQR, and standard drug Acarbose, Glibenclamide)

Compounds Name	Score of Docking	Glide Emodel	Energy of Glide	Interconnecting Residues
Coniferol	-7.367	-47.747	-33.039	Asp197, Glh233, Trp59, Gln63, Glu60, Ala198, Arg195, Pro64
Bisdemethoxycurcumin	-7.293	-58.042	-40.426	Asp197, Asp300, Asp96, Hip305, Gln63, Ala198, Hie299, Glu60
Desmethoxycurcumin	-7.119	-63.998	-45.708	Glh233, Asp197, Gln63, Asp300, Cys103, Pro64, Thr163, Leu165
Curcumin	-7.093	-65.341	-46.407	Glh233, Asp197, Gln63, His201, Val98, Ser199, Asp300, Leu162
Acarbose	-6.808	-53.565	-37.845	Asp197, Asp300, Asp356, Trp59, Ile51, Hip305, Gly306
Glibenclamide	-4.525	-63.994	-46.77	Gln63, Hip305, Trp59, Thr163

Molecular docking was used to examine the means by which the components of C. caesia bind to the associated receptors. A molecular docking research was carried out using C. caesia's compounds and a common drug at the active site of alpha-amylase (PDB ID: 4GQR) (acarbose, glibenclamide). The 2-D ligand interaction diagrammatic viewpoint suggests that the oxygen atom of the compound coniferol amide nucleus formed interactions of hydrogen alongwith Trp59, Gln63, and Asp197 residues of amino acid. With oxygen atoms of the molecules Bisdemethoxycurcumin and Desmethoxycurcumin amide nucleus, amino acid residues Asp300, Asp197, and Gln63 formed hydrogen bonds.

Hydrogen bonds were formed between the oxygen atoms in the amide nucleus of the molecule

curcumin and the amino acid residues Asp197, Gln63, and water.Hydrogen bonds were formed between the oxygen atoms of the amide nucleus of the common drug acarbose and the amino acid residues Asp197, Gln63, Asp300, and Asp356. The figures for glide energy, docking scores, and glide emodel were displayed negatively.

The affinity of the ligand for interacting to the receptor increases as the score of docking decreases. Docking data for the top four substances (coniferol, bisdemethoxycurcumin,

desmethoxycurcumin, and curcumin), as well as the reference drug, are displayed in Table 3. The docked molecules coniferol, bisdemethoxycurcumin, desmethoxycurcumin, curcumin, and acarbose are shown in Figures 1, 2, 3, 4, 5 and 6 together with their respective binding surfaces and ligand interaction diagrams. The 2-D ligand interaction diagrammatic perspective reveals that these compounds bind with homologous residues of amino acid and have the same homology like regular acarbose

.
Binding surface & 2D interaction diagram of compounds of *C.caesia* using PDB ID: 4GQR
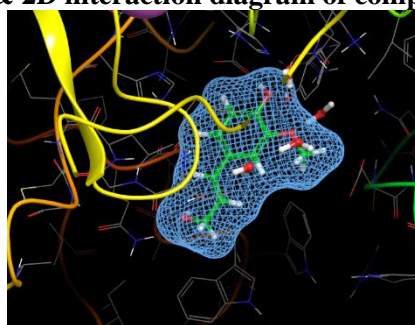
Figure1:Coniferol
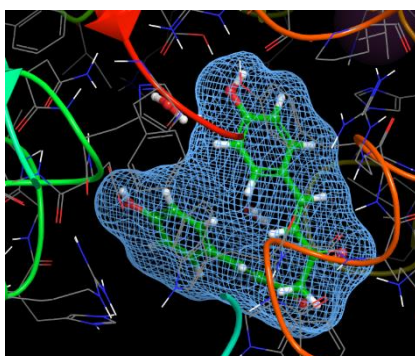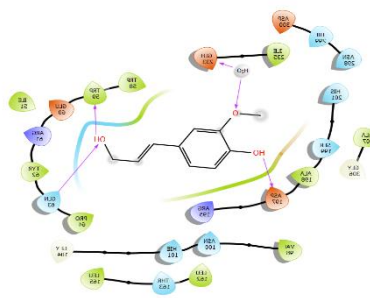
Figure 2: Bisdemethoxycurcumin
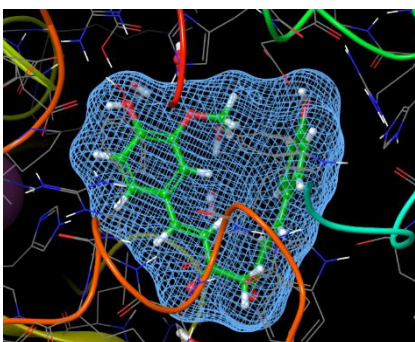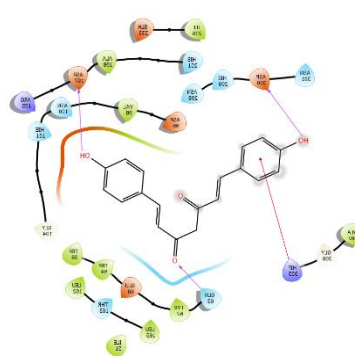
Figure 3: Desmethoxycurcumin

Fig 4: Curcumin

Figure 5: Acarbose

Figure 6: Glibenclamide

Table 4: Docking score of the most active components using PDB ID: 6C9X, and reference drug Acarbose, Glibenclamide

Compounds Name	Docking data	Glide Emodel	Glide Energy	Interrelating Residues
Xanthinin	-8.167	-50.464	-32.250	Asp420, Hie478, Asp197, Ala480, Met308, Trp271, Pro75, Phe453
Dibutyl phthalate	-7.185	-39.034	-27.924	Hie478, Ash26, Met308, Phe314, Arg476, Glu481, Tyr85, Trp417
Aconerol	-6.778	-38.604	-29.398	Hie478, Asp307, Met308, Glu481, Arg476, Gly419, Ash236, Ile234
Desmethoxycurcumin	-6.739	-68.918	-48.481	Trp169, Asp197, Arg404, Ala269, Hie478, Lys348, Met347, Trp271
Acarbose	-6.205	-76.306	-60.952	Hie478, Asp73, Glu481, Arg404, Asp197, Asp420, Asp449, Ser167
Glibenclamide	-4.727	-66.804	-50.824	Asp455, Arg404, Lys 422

Molecular docking was used to examine the means by which the compounds of *C. caesia* bind to the associated receptors. We performed a

molecular docking analysis of *C. caesia* compounds and a conventional drug on the active site of alpha-glucosidase (PDB ID: 6C9X)

(acarbose). According to the 2-D ligand interaction, the oxygen atom of the molecules Xanthinin and Aconerol amide nucleus established hydrogen bonds with Hie478 residues of amino acid. Hydrogen bonds were produced between the amino acid residues of Hie478, Ash236, and water and the Dibutyl phthalate amide nucleus of the molecule. The oxygen atoms in the amide nucleus of desmethoxycurcumin and the residue of the amino acid Asp197 created hydrogen bonds.The amino acid residues Asp197, Glu481, Asp73, Arg404, Asp420, and Hie478 formed hydrogen bonds with the oxygen atoms of the amide nucleus of the common medication acarbose. The docking scores, glide energy, and glide emodel numbers

were displayed negatively. The ligand's affinity for binding to the receptor increases with decreasing docking score. The top four compounds (Xanthinin, Dibutyl phthalate, Desmethoxycurcumin, and Aconerol), as well as the reference drug, are shown in Table 4 along with their docking data.Figures 7, 8, 9, 10, 11and 12 show the docked molecules Xanthinin, Dibutyl phthalate, Desmethoxycurcumin, Aconerol, and acarbose's respective binding surface and ligand interaction diagram.According to the 2-D ligand interaction diagrammatic perspective, these compounds have the same homology as regular norfloxacin by interacting with homologous amino acid residues.

Binding surface and 2D interaction diagram of compounds using PDB ID: 6C9X
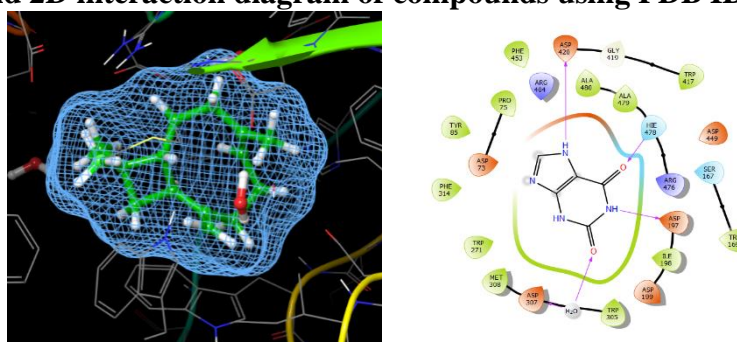

Figure 7: Xanthinin
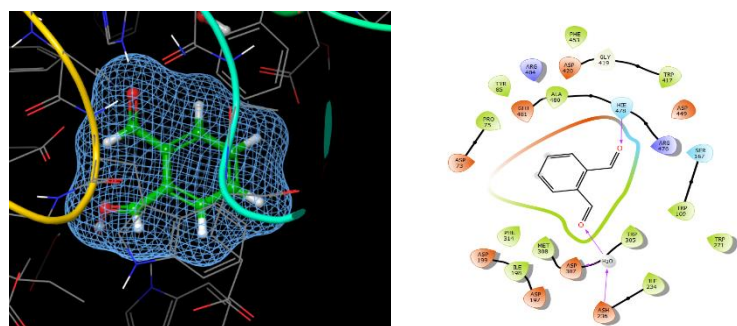
Figure 8: Dibutyl phthalate
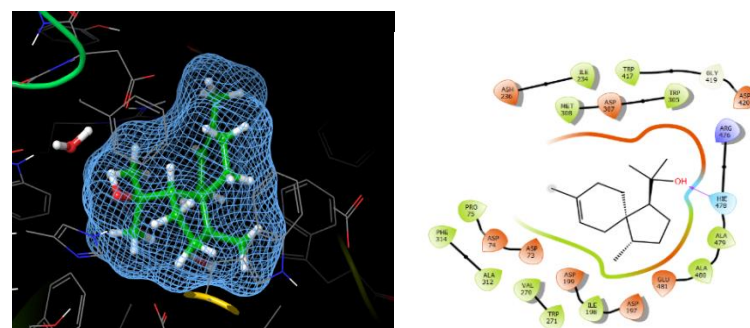
Figure 9: Aconerol
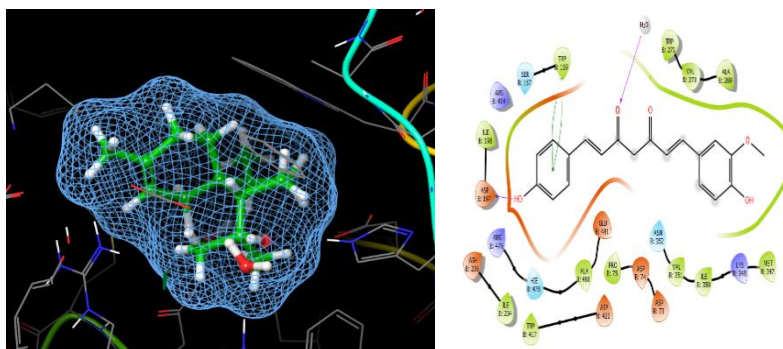
Figure 10: Desmethoxycurcumin
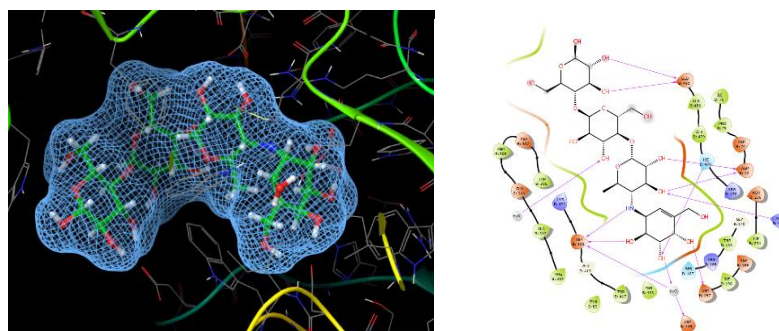
Figure 11: Acarbose
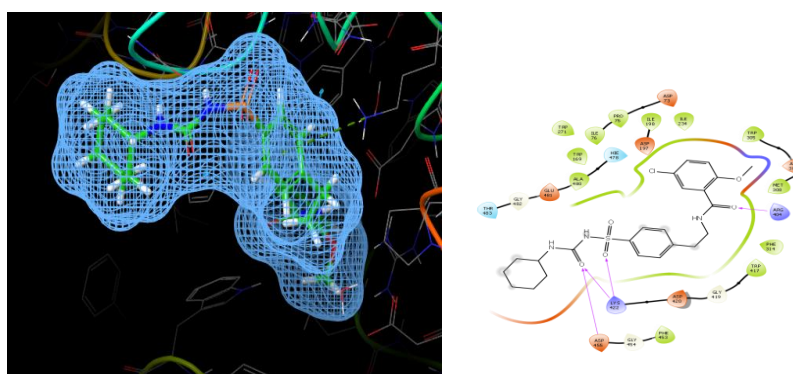
Figure 12: Glibenclamide

Table 5: Docking score of the most active compounds using PDB ID: 1ITU, and standard drug Acarbose, Glibenclamide

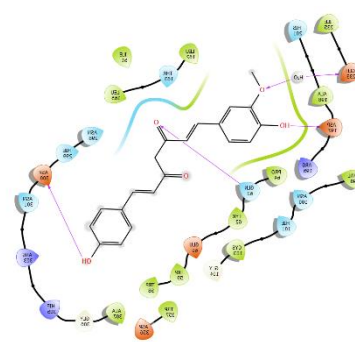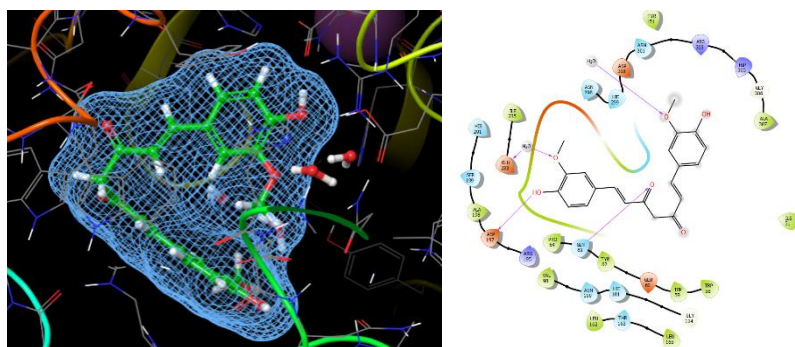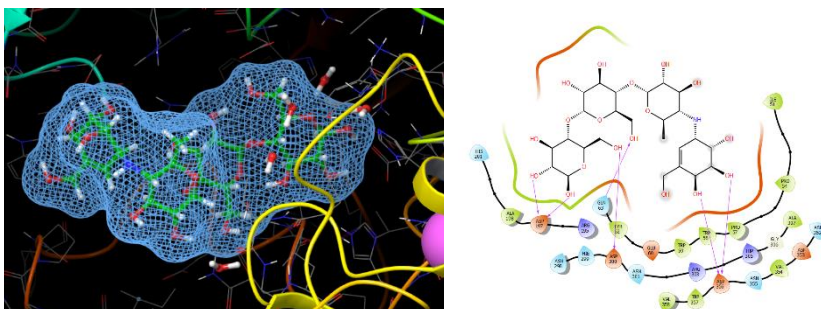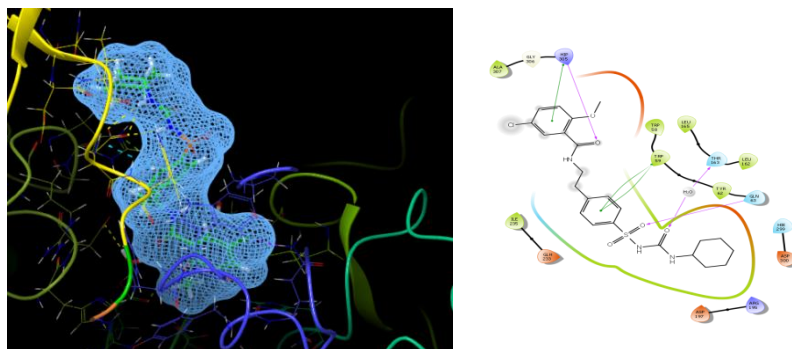| Compounds Name	Docking Score	Glide Emodel	Glide Energy	Residues of interaction
Dibutyl phthalate	-5.391	-37.839	-25.779	Asp288, Arg230, Zn402, Hie152, Tyr252, Val292, Pro293, Arg294
Arglabin	-5.305	-39.682	-27.996	Hie152, Val292, Pro293, Tyr252, Asn250, Gly291, Gln26, Asp22
Ivalin	-5.087	-40.858	-31.292	Tyr68, Hie152, Asp29, Cys71, Val292, Ser153, His20
Terpinen-4-ol	-4.933	-25.684	-19.274	Asp288, Gly291, His20, Thr9, Tyr68, His198, Gln26, Cys71
Acarbose	-4.697	-57.210	-45.799	Hie152, Cys71, Asp72, Asp288, Tyr68, Thr69, Ser153, Asp290
Glibenclamide	-6.535	-77.075	-51.184	Arg230, Hie152, Gly291, Tyr252

Molecular docking was used to examine the means by which the components of *C. caesia* bind to the associated receptors. A molecular docking study of *C. caesia* compounds and a common drug was carried out using the active site of dipeptidase (PDB ID: 1ITU) (acarbose). From a 2-D ligand

interaction diagrammatic standpoint, the oxygen atom of compounds' Ivalin amide nucleus formed hydrogen connections with Hie152 and Tyr68 amino acid residues. The Gly291 and Asp288 amino acid residues made hydrogen bonds with the Terpinen-4-ol amide compound's oxygen

atom.The amino acid residues Hie152, Arg230, and Zn402 formed hydrogen bonds with the Dibutyl phthalate amide nucleus of the molecule. Hie152 amino acid residues formed hydrogen bonds with the amide nucleus of compound arglabin's oxygen atoms. The amino acid residues Cys71, Asp72, Hie152, Tyr68, and Asp288 formed hydrogen bonds with the oxygen atoms of the amide nucleus of the common medication acarbose. The docking scores, glide energy, and glide emodel numbers were displayed negatively. The ligand's affinity for binding to the receptor increases with decreasing docking score.The top

four compounds (Ivalin, Dibutyl phthalate, Terpinen-4-ol, and Arglabin) as well as the reference drug are shown in Table 5 along with their docking data. Figures 13, 14, 15, 16, 17 and 18 show the docked molecules Ivalin, Dibutyl phthalate, Terpinen-4-ol, Arglabin, and acarbose's binding surface and ligand interaction diagram, respectively. According to the diagrammatic viewpoint of 2-D ligand interaction, these compounds interact with homologous residues of amino acid to have the same homology as regular Acarbose.

Binding surface and 2D interaction diagram of compounds using PDB ID: 1ITU
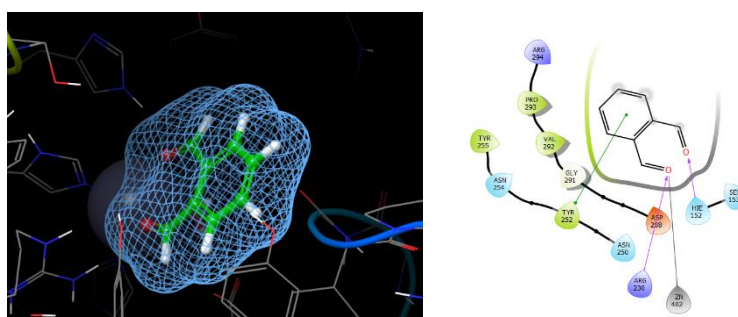

Figure 13: Dibutyl phthalate
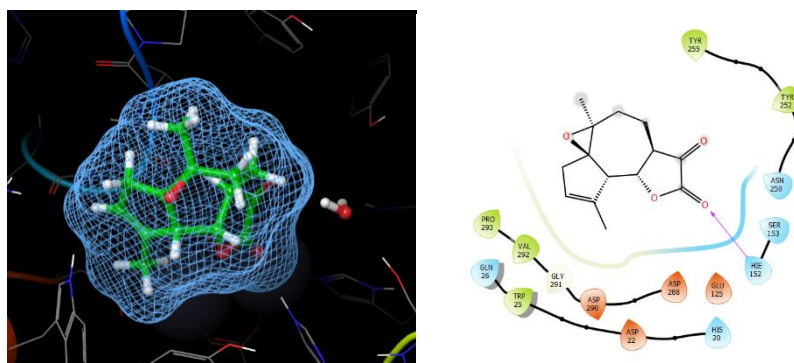
Figure 14: Arglabin
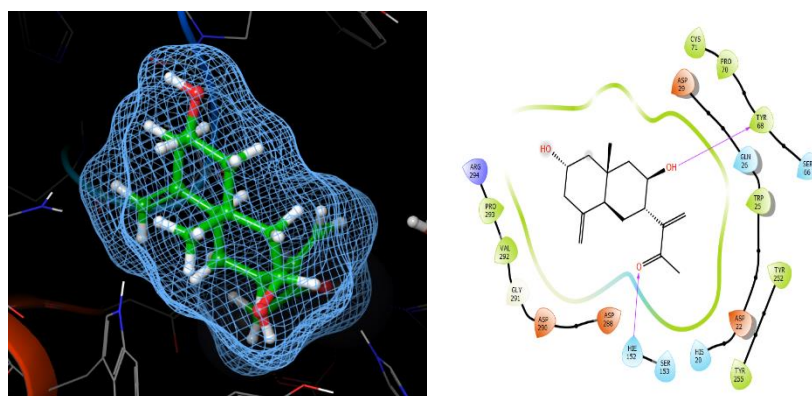
Figure 15: Ivalin
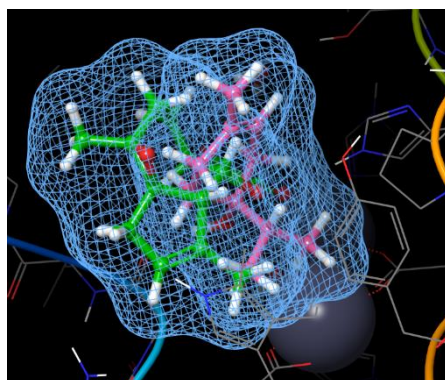
Figure 16: Terpinen-4-ol
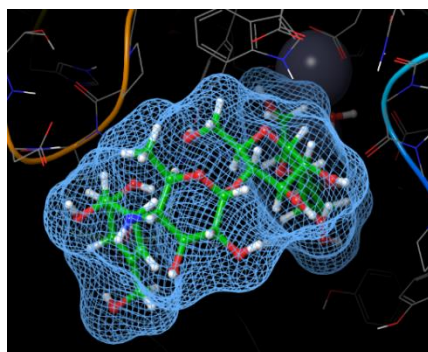
Figure 17: Acarbose
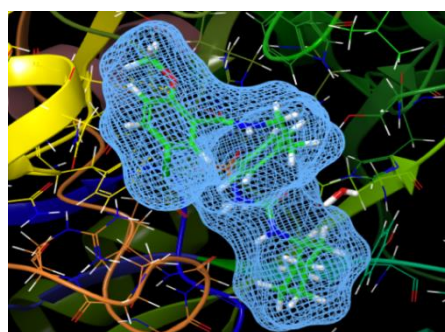
Figure 18: Glibenclamide

ADME Study

Using the QikProp module for Schrodinger v 13.1, the ADME properties of the compounds of C. caesiagiven were identified. Aconerol, Arglabin, Bisdemethoxycurcumin, Coniferol, Curcumin, Desmethoxycurcumin, Dibutyl phthalate, Ivalin, Terpinen-4-ol, and Xanthinin are some of the best active complexes whose ADME data are summarised in Table 6. The compounds Aconerol, Arglabin, Bisdemethoxycurcumin, Coniferol,

Curcumin, Desmethoxycurcumin, Dibutyl phthalate, Ivalin, Terpinen-4-ol, and Xanthinin all adhered to the Lipinski rule of five.According to the conclusions, the compounds Aconerol, Arglabin, Bisdemethoxycurcumin, Coniferol, Curcumin, Desmethoxycurcumin, Dibutyl phthalate, Ivalin, Terpinen-4-ol, and Xanthinin adhere to rule of Lipinski, suggesting that thecompounds can be employed as model molecules for further investigation.

Table 6: ADME scoring of the most active constituents of *C. caesia*

Compounds Name	MW	donorHB	accptHB	QPlogPo/w	QPlogBB	Oral absorption in humans	Rule of Five
Aconerol	222.3	1	0.7	4.0	0.2	3	0
Arglabin	248.2	1	5.7	1.1	-0.2	3	0
Bisdemethoxycurcumin	308.3	2	3.2	3.4	-2.0	3	0
Coniferol	180.2	2	3.2	1.3	-0.6	3	0
Curcumin	368.3	2	4.7	3.7	-2.1	3	0
Desmethoxycurcu	338.3	2	4.0	3.5	-2.1	3	0

	min						
Dibutyl phthalate	134.1	0	4.0	0.2	-0.5	3	0
Ivalin	264.3	2	5.4	1.8	-0.7	3	0
Terpinen-4-ol	154.2	1	0.7	2.9	0.2	3	0
Xanthinin	152.1	3	5.0	-1.8	-1.0	2	0

- ✓ Molecular weight: 500 Da or less.
- ✓ Donor of hydrogen bonds (Accepted Maximum: 5)
- ✓ Acceptor of hydrogen bonds (Accepted Limit: 10)
- ✓ Log P low than 5.
- ✓ Human oral absorption is rated as low, medium, or high using 1, 2, or 3.
- ✓ QPlogBB values vary from -3.0 to 1.2.

CONCLUSION

This study used a variety of computational methods, including molecular docking, ADME investigations, and compounds of *C. caesia* against alpha-glucosidase, alpha-amylase, and dipeptidase receptor. Coniferol, Bisdemethoxycurcumin, Desmethoxycurcumin, and curcumin have the highest docking scores against protein alpha-amylase according to molecular docking studies (PDB ID: 4GQR). With respect to protein alpha-glucosidase, compounds Xanthinin, Dibutyl phthalate, Desmethoxycurcumin, and Aconerol have the highest docking scores (PDB ID: 6C9X). Against protein dipeptidase, compounds Ivalin, Dibutyl phthalate, Terpinen-4-ol, and Arglabin had the best docking scores (PDB ID: 1ITU).The compounds Aconerol, Arglabin, Bisdemethoxycurcumin, Coniferol, Curcumin, Desmethoxycurcumin, Dibutyl phthalate, Ivalin, Terpinen-4-ol, and Xanthinin all exhibit an excellent ADME profile depnds upon the results of molecular docking and binding interaction research. These substances (Aconerol, Arglabin, Bisdemethoxycurcumin, Coniferol, Curcumin, Desmethoxycurcumin, Dibutyl phthalate, Ivalin, Terpinen-4-ol, and Xanthinin), according to the study, could be used as lead structures for further studies on anti-diabetic resistance.

CONSENT FOR PUBLICATION
Not applicable

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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Declared none.

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