STM JOURNALS

International Journal of
Biochemistry and Biomolecule Research

Volume 2, Issue 1, 2024
January—June
DOI (Journal): 10.37591/IJBBR

https://journals.stmjournals.com/ijbbr

Research IJBBR

Anti-hyperglycemia Effects of Plant Secondary Metabolites Towards PKA/CREB Pathway Activation in Diabesity

Bhumica Kiran*

Abstract

Objective: *Diabesity, the amalgamation of diabetes and obesity, presents a significant global health challenge. This research carefully examines how plant secondary metabolites influence glucose regulation in diabetes using the PKA/CREB pathway, paying particular attention to diabesity—the combination of diabetes and obesity. Understanding the complex ways in which these metabolites affect metabolic health will help to identify new treatment approaches for managing diabetes and its associated problems. By conducting a thorough analysis, this research aims to provide essential insights into the creation of focused interventions that will ultimately improve the management of metabolic disorders in general and the health of the general public by addressing the various challenges presented by obesity.* ***Methods:*** *The study aimed to evaluate the efficacy of various phytochemicals against diabetes using computational techniques to target the proteins 4uj1 and 6e99. Protein structures were validated using PDBsum and BIOVIA Discovery Studio. Molecular docking, facilitated by PyRx, utilized data from PubChem and molecular structures from Indian medicinal plants. Ligands were pharmacologically assessed using ADMET filters. This comprehensive approach, integrating multiple data sources and computational methods, offers deep insights into potential anti-diabetic medications. The use of advanced technologies such as molecular docking and protein structural validation enhances our understanding of the therapeutic potential of natural compounds in diabetes management. The results highlight the importance of combining traditional knowledge with modern scientific techniques to develop effective treatments, suggesting that compounds from Indian medicinal plants may offer novel strategies for treating diabetes and related metabolic disorders.* ***Results:*** *Molecular docking experiments identified Ginkgolides, Nimbin, tetrandrine, emblicanin A, and ginsenosides as ligands with the lowest binding affinities to the target proteins, indicating their potential as anti-hyperglycemic agents.* ***Conclusion:*** *Nimbin, due to its low binding affinity for the proteins 4uj1 and 6e99, shows promise for diabetes therapy through the PKA/CREB pathway. This finding underscores the significance of Nimbin in ongoing diabetes research and clinical trials, highlighting its potential for developing new treatment strategies.*

***Author for Correspondence**
Bhumica Kiran
E-mail: bhumicakiran26@gmail.com

Student, Department of Biotechnology, Ramaiah University of Applied Sciences, Mathikere, Bengaluru, Karnataka, India

Received Date: April 01, 2024
Accepted Date: May 23, 2024
Published Date: August 24, 2024

Citation: Bhumica Kiran. Anti-hyperglycemia Effects of Plant Secondary Metabolites Towards PKA/CREB Pathway Activation in Diabesity. International Journal of Biochemistry and Biomolecule Research. 2024; 2(1): 33–50p.

Keywords: Diabetes, diabetes mellitus, Type 2 DM, Type 1 DM, obesity, PKA/CREB pathway, anti-hyperglycemia

INTRODUCTION

Egyptians were the first to record diabetes, which is defined as weight loss and polyuria. However, Aertaeus, a Greek physician, first coined the term diabetic mellitus (DM). The Latin word mellitus means “honey” (a reference to sweetness), and the

Greek word diabetes means "to pass through." As the most common endocrine disorder, it affects approximately 100 million people worldwide, or 6% of the world's population [1]. Variations in blood glucose levels are caused by the inability of the pancreas or insufficient production of insulin. There are two types of diabetes mellitus: Type I insulin-dependent diabetes (IDDM) and Type II non-insulin-dependent diabetes (NIDDM). Type I diabetes is an autoimmune disease that results in a localized inflammatory response in and around islets, which is followed by the selective death of insulin-secreting cells. This is in contrast to Type II diabetes, which is characterized by peripheral insulin resistance and diminished insulin production [2]. Diabetes and obesity were found to be strongly associated. Obesity is a significant risk factor for type 2 diabetes and pre-diabetes mellitus. Obesity is a multifaceted complex disorder. Approximately one-third of the world's population has been categorized as overweight or obese, following a two-fold increase in the incidence of overweight and obesity worldwide since 1980. While numerous definitions of obesity exist, the most widely accepted adhere to the WHO's body mass index (kg/m^2) recommendations. There are three main classes of obesity: class 1 (30.0–34.9 kg/m^2), class 2 (35.0–39.9 kg/m^2), and class 3 (R40 kg/m^2). Although obesity rates have increased across all age groups and sexes, older adults and women are more likely than other groups to be fat. This trend was observed regardless of geographic location, ethnicity, or socioeconomic status [3]. The word "diabesity," coined in the 1970s by Sims and colleagues, refers to the strong association between obesity and type 2 diabetes. Diabetes is also known to be dependent on obesity. It has recently been recognized as a severe public health concern that is growing into an epidemic [4]. A considerable amount of clinical research suggests that being overweight or obese is associated with an increased risk of developing type 2 diabetes. Mostly attributed to changes in human behavior, especially sedentary lives, and the spread of the Western diet, along with genetic susceptibility. Diabetes and obesity are crucial components of metabolic syndrome [5].

The pathogenesis of diabetes is related to various signaling pathways. Concerns over the dysregulation of protein kinase A (PKA) signaling in relation to obesity, a metabolic disorder with grave implications for public health, are growing. PKA is an essential enzyme in cellular signal transduction that affects several physiological processes such as metabolism and energy homeostasis. Dysregulation of PKA, specifically in Regulatory Subunit 2 B (R2B), has been linked to obesity. Variations in PKA activity may affect metabolic dysfunction, insulin resistance, and abnormal fat storage. Determining whether specific biochemical pathways are influenced by dysregulated PKA signaling may help to identify new targets for the treatment of obesity-linked metabolic diseases. The data may provide insights into the complex interplay among genetic, environmental, and molecular factors that contribute to the etiology of obesity and facilitate the creation of customized and targeted obesity management strategies. The brain is one of the tissues that depend on glucose circulation and is maintained by cells. By controlling glucose homeostasis, insulin, and glucagon lower hyperglycemia and maintain blood glucose levels during fasting [6–9]. The synthesis of glucose from non-carbohydrate substrates, such as lactate, pyruvate, glycerol, and glucogenic amino acids, is known as gluconeogenesis. Enzymes including fructose 1,6-bisphosphatase, phosphoenolpyruvate carboxykinase, and pyruvate carboxylase are necessary for this process. Glucagon triggers the expression of many enzymes when it binds to its receptor, initiating the protein kinase A (PKA) cascade that ends in the nucleus and activates a nuclear transcription factor known as CREB. By attaching to the cAMP-response element (CRE) DNA sequence, CREB stimulates the synthesis of gluconeogenic enzymes. According to previous research, people with obesity and type 2 diabetes have higher plasma glucagon concentrations, which may cause hyperglycemia. A potentially useful treatment involves blocking the CREB activity to target glucagon expression and stop gluconeogenesis [10].

Blood glucose levels that are higher than usual in an individual can be referred to as pre-diabetes; however, the individual's blood glucose levels do not match the criteria to be diagnosed with diabetes. Diabetes mellitus is greatly increased by obesity, and weight reduction lowers vascular risk factors and blood glucose regulation. Treatment options for obese people with diabetes include anti-obesity medications, insulin-resistant patients' reduced insulin requirements, lifestyle modifications, and

managing risk factors such as dyslipidemia and arterial hypertension. When necessary, oral medications should be administered in addition to insulin. In extreme circumstances, weight loss is required to improve glycemic control and address related risk factors. Weight loss programs that are aggressive, such as extremely low-calorie diets and bariatric surgery, should be evaluated as part of a long-term multidisciplinary plan [11–13].

Diabetes can be treated or prevented with synthetic medications; however, these medications have negative effects. Currently, there is great interest in identifying natural chemicals that work because of this problem and their high cost. Herbal remedies have been the subject of numerous investigations in recent years, and these substances have been suggested as treatments for several incurable conditions, including cancer, atherosclerosis, cardiovascular disease, and neurological problems. These circumstances include a variety of changes such as modifications of the redox state. Antioxidant-active medicinal herbs can counteract these circumstances and have long been regarded as a beneficial source of health promotion. Patients with diabetes used traditional medicine and medicinal herbs before anti-diabetic medications and insulin were discovered. Many methods that affect blood sugar levels can be used by plants. Certain individuals may possess insulin kinase, while others may suppress insulinase activity, and others may promote the growth of pancreatic β cells. Plant fibers may potentially impact blood glucose levels by obstructing the absorption of carbohydrates. Herbs and secondary metabolites are useful for the treatment and control of diabetes [14].

METHODS

Retrieval of Ligands

To treat diabetes and obesity, secondary metabolites, such as semaglutide and meglitinides, have been selected from the phytochemical components of different plants. The current study included 100 phytocompounds. The IMPPAT (Indian Medicinal Plants, Phytochemistry and Therapeutics) database (https://cb.imsc.res.in/imppat/) was used to identify the potential ligands. The canonical smiles of all ligands selected for the current experiment were recorded. The top 35 ligands were retrieved from PubMed (https://pubchem.ncbi.nlm.nih.gov/). SDF format.

Retrieval of Proteins

The 3-dimensional structures of the proteins were downloaded from the RCSB PDB database (https://www.rcsb.org/). The crystal structures of PKA (PDB ID:4uJ1) and CREB (PDB ID: 6e99) were downloaded from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) (https://www.rcsb.org/).pdb format and resolved using the X-ray diffraction method. The resolution of the protein downloaded is 1.768 Å for PKA(4uJ1) and 1.88 Å for CREB (6e99). Missing residues in the protein structures were modeled using the SWISS-MODEL web server (https://swissmodel.expasy.org/). The proteins were purified before docking by eliminating the heteroatoms, ligand groups, and water molecules, retaining only the A chains from the crystal structure of the proteins, and polar hydrogens were added to the purified structures in the BIOVIA Discovery Studio software. The purified proteins were further stored. pdb files.

Protein Structure

Understanding 3-dimensional structures is essential for molecular docking as they determine how the ligands interact with proteins. The purified structures were validated using the web server PDBsum (http://www.ebi.ac.uk/thornton-srv/databases/pdbsum/Generate.html) and DS BIOVIA Discovery Studio.

Molecular Docking

Molecular docking was used as the main investigative technique. Using PyRx, a virtual screening program, chemical libraries can be tested against possible therapeutic targets during the computational drug development process. Using PyRx, a molecular docking engine was used to dock the 35 screened ligands. PyRx was used to independently associate ligands with the target proteins. Plant

phytocompounds were introduced as ligands to PyRx after purified proteins were uploaded as macromolecules. After the loaded ligands were transformed into the pbqt format, a universal force field was applied to minimize the energy. The following grids were generated for each target protein: 4UJ1 (Center X:27.302 Y:2.0269 Z:2.6953; Dimensions (Angstrom) X:51.8009 Y:66.1027 Z:48.5558) and 6E99 (Center X: -8.6696 Y:13.4885 Z: -21.6106; Dimensions (Angstrom) X:51.9453 Y:47.8900 Z:65.8024). After the ligands and target proteins were docked, the binding affinities of relevant docking interactions were assessed. The ligands in PyRx underwent nine distinct conformational modifications to obtain the highest binding scores. The binding affinity associated with zero values of Root Mean Square Deviation (RMSD) was shown to be the ideal docking conformation because these conformations have the lowest binding scores. The best-binding complex for each target protein was determined by selecting the top five conformations with the lowest binding affinities. After retrieving and saving the docked ligand structures as PDB files, the interaction was visualized using DS BIOVIA Discovery Studio.

Visualization

The structure visualization program BIOVIA Discovery Studio was used to display the output (docked structures) of PyRx. The BIOVIA Discovery Studio Visualizer was used to view the best-binding conformations obtained in the PDB format. We examined the two- and three-dimensional models, as well as the non-bond interactions.

Pharmacological Studies

ADMET analysis, which evaluates attributes such as physiochemical properties, medicinal chemistry, absorption, distribution, and toxicity, helps in the process of finding new drugs. ADMET traits play a major role in determining drug-likeness characteristics and pharmacological activity and are possible candidates for medicinal development. ADMET analysis was performed using the web server ADMETlab 2.0 (https://admetmesh.scbdd.com). Based on the docking data, the ligands with the best-binding affinities were selected for ADMET analysis. The canonical SMILES of the top five ligands were acquired from PubChem and submitted for ADMET evaluation via the ADMETlab 2.0 portal.

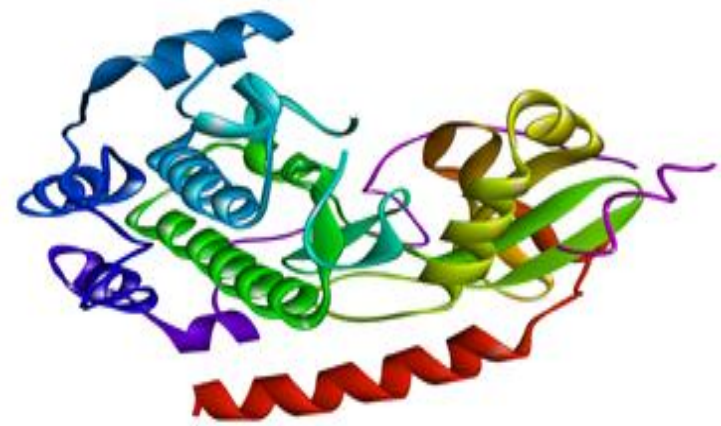
RESULTS

Protein Structure Analysis

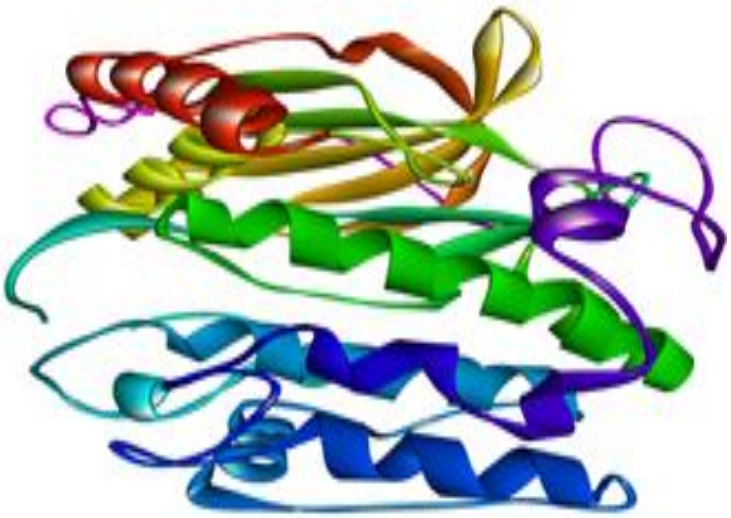
In light of the findings of this research, we were successful in extracting 100 ligands (phytochemicals) to treat diabetes and obesity. The target proteins 4UJ1 and 6E99 were downloaded from the PDB website. Later, this protein was purified using BIOVIA, a bioinformatic application. Figure 1(a)–(f) shows the evaluation of the secondary structures of proteins 4uj1 and 6e99. Figure 2 and Figure 3 show the secondary structures of proteins 4UJ1 and 6e99, respectively. The next phase involved verifying the secondary structures of the protein, the Ramachandran plot, and the hydropathy plot using PUBSUM. Table 1 shows the Ramachandran Plot Statistics and Secondary structure summary of 4uj1 and 6e99.

Table 1. Ramachandran plot statistics and secondary structure summary of protein 4uj1 and 6e99.

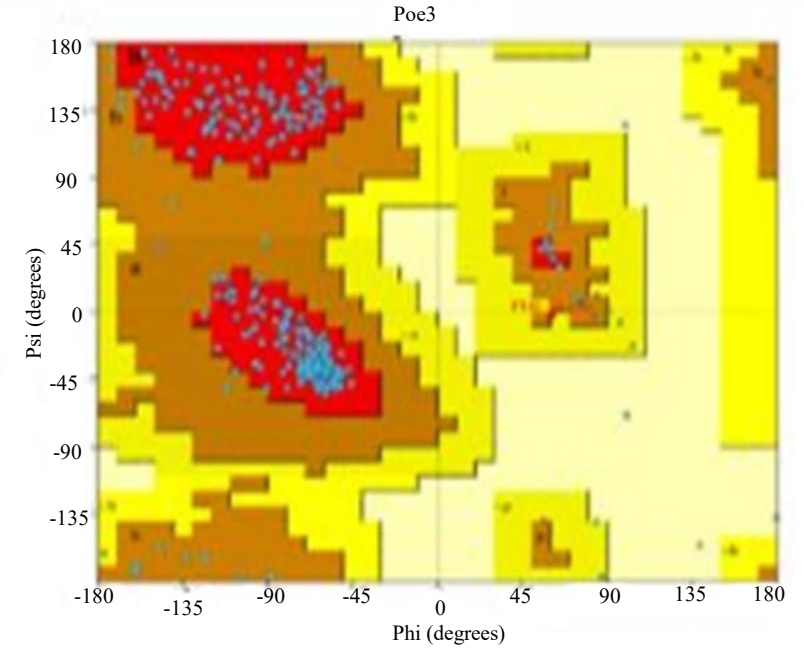
Structural analysis Ramachandran plot statistics	**Protein I (4uj1) Number of residues**	**Protein II (6e99) Number of residues**
Most favored regions [A, B, L]	269	267
Additional allowed regions [a, b, l, p]	25	24
Generously allowed regions [~a, ~b, ~l, ~p]	1	0
Disallowed regions [XX]	0	0
Secondary structure summary	**Protein I (4uj1)**	**Protein II (6e99)**
Strand	49 (14.6%)	49 (14.8%)
Alpha helix	110 (32.8%)	107 (32.3%)
3-10 helix	10 (3.0%)	10 (3.0%)
Other	166 (49.6%)	165 (49.8%)



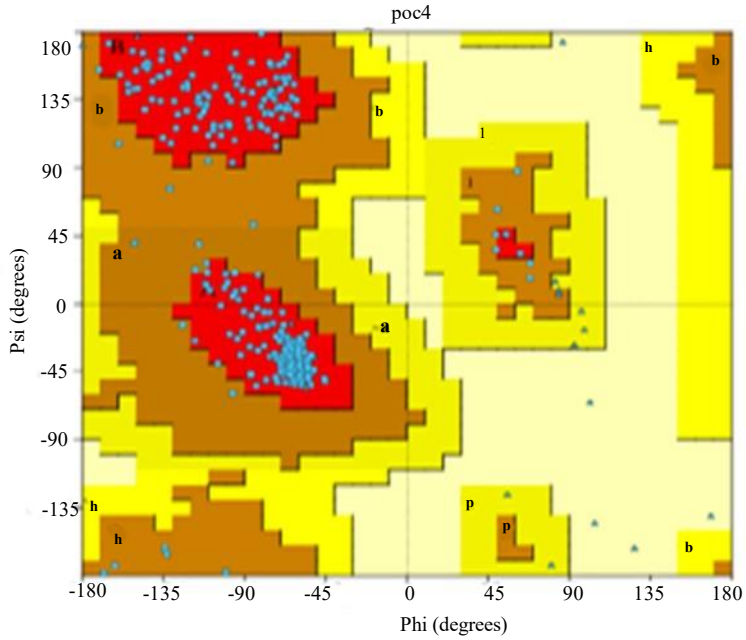
(a) Purified PKA structure (PDB ID:4uj1)



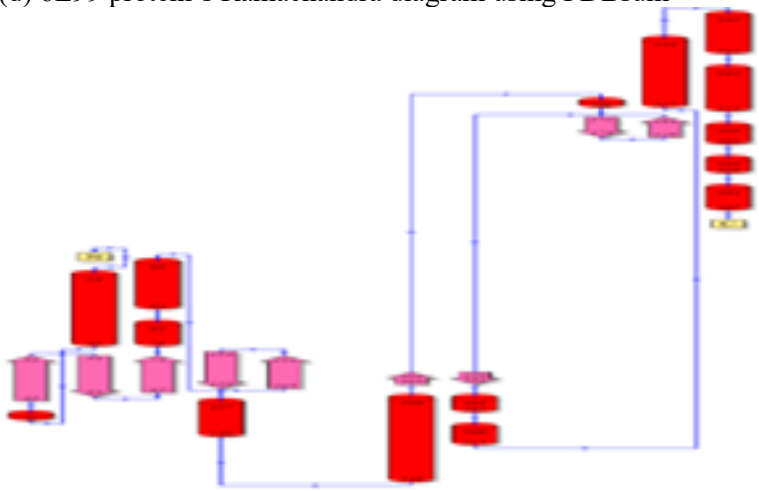
(b) Purified PKA structure (PDB ID:6e99).



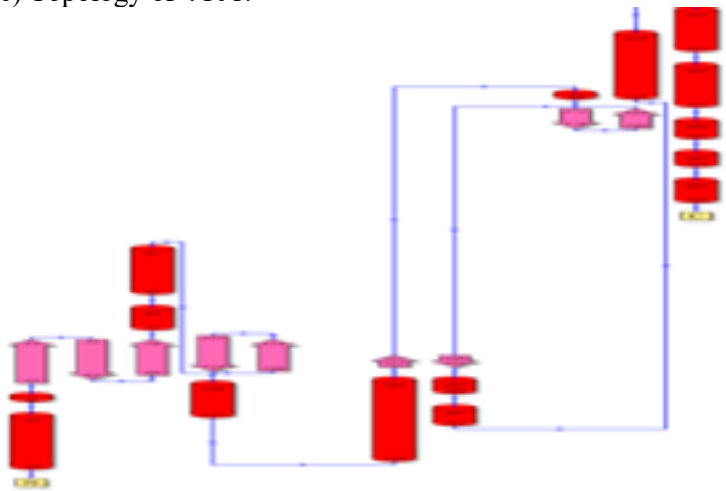
(c) 4UJ1 protein's Ramachandra diagram PDBsum



(d) 6E99 protein's Ramachandra diagram using PDBsum



(e) Topology of 4UJ1.



(f) Topology of protein 6E99

Figure 1. (a-f) Evaluation of Proteins 4uj1 and 6e99's secondary structures.

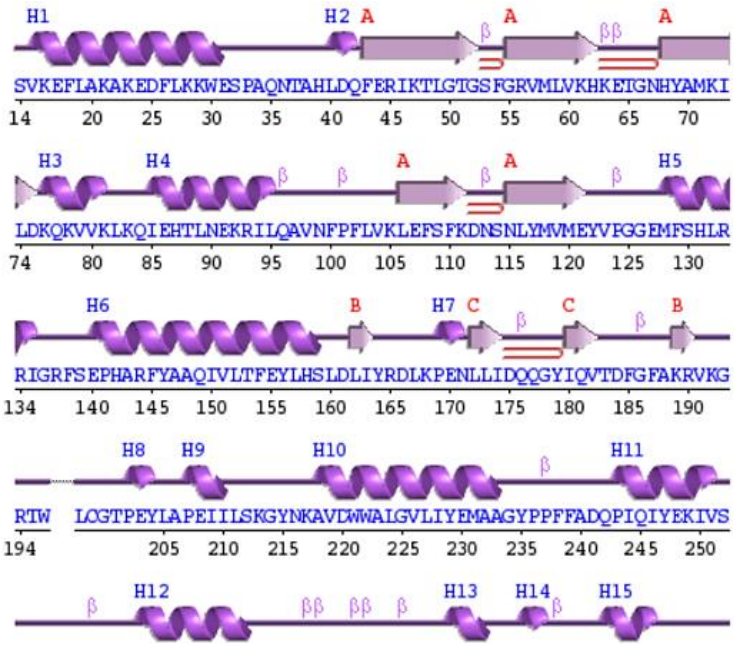


Figure 2: Secondary structure of protein 4UJ1.

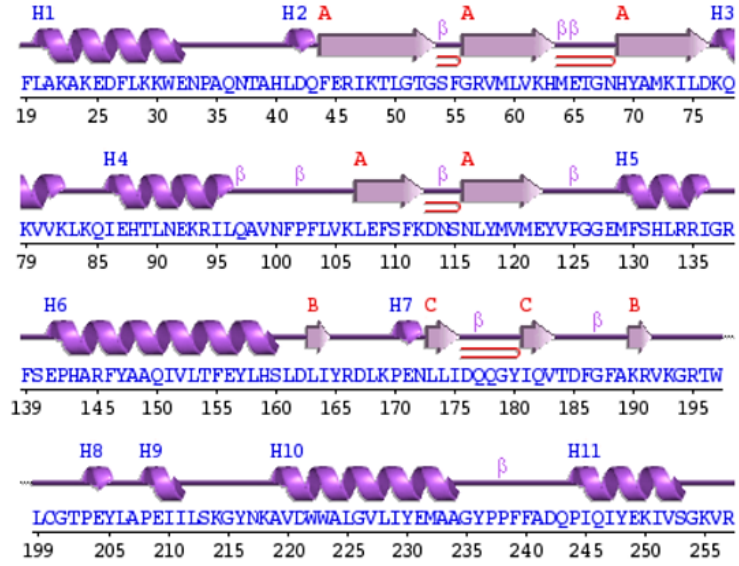


Figure 3. Secondary structure of protein 6E99.

Molecular Docking

Using PyRx, a molecular docking engine was used to dock the 35 screened ligands. PyRx was used to independently associate ligands with the target proteins. The target proteins 4UJ1 (Center X:27.302 Y:2.0269 Z:2.6953; Dimensions (Angstrom) X:51.8009 Y:66.1027 Z:48.558) and 6E99 (Center X: -8.6696 Y:13.4885 Z: -21.6106; Dimensions (Angstrom) X:51.9453 Y:47.8900 Z:65.8024) each had the following grids, as shown in Figures 4 and 5.

PyRx ligands undergo nine conformational changes to achieve maximum binding scores. The binding affinity associated with zero RMSD values was shown to be the ideal docking conformation because they showed the lowest binding scores of all conformations. The ideal binding complex for each target protein was selected from the top five conformations with the lowest binding affinities. Tables 2 and 3 show the docking scores of 4UJ1 and 6E99 proteins, respectively, with the selected ligands.

Visualization

The Dassault Systems BIOVIA Discovery Studio Visualizer was used to visualize selected ligands, obtain two- and three-dimensional models, and collect amino acid residues, bond distances, and interaction details. Figures 6 and 7 show the 2D and 3D structures of the selected ligand of 4UJI. Similarly, Figures 8 and 9 show the 2D and 3D structures of the selected ligand of 6E99.

Pharmacological Studies

The drug's gastrointestinal absorption in humans, blood-brain permeation level, glycoprotein permeability, and solubility were all assessed during ADME testing. The blood–brain barrier (BBB) is a factor that determines a drug candidate's ability to pass through. Medicines cannot be synthesized without this knowledge. High gastrointestinal adsorption is crucial for drug effectiveness. Oral drugs should have excellent solubility to maximize therapeutic effects. The top five ligands' SMILES were evaluated using ADMET Lab 2.0, as shown in Tables 4–10.

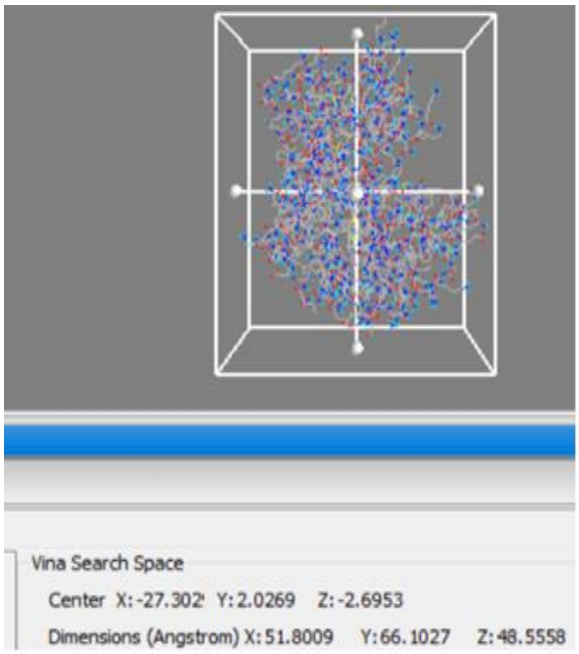


Figure 4. Grid for the protein 4UJ1.

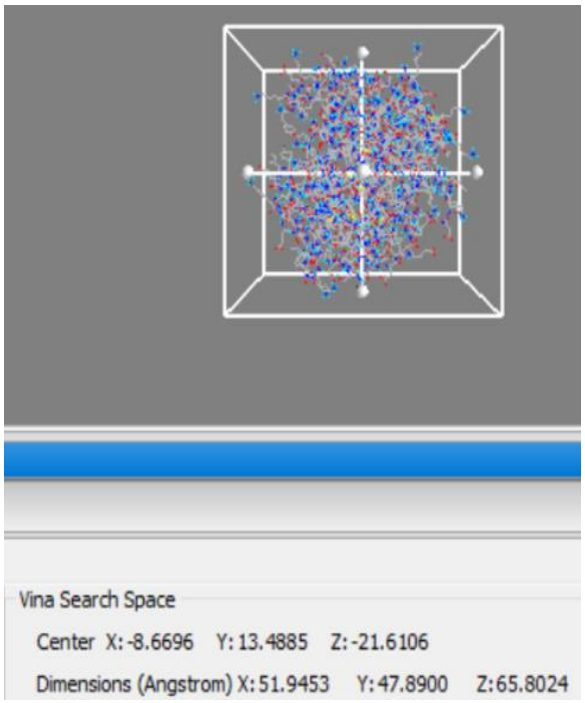


Figure 5. Grid for the protein 6E99.

Table 2. Docking score of 4UJ1 protein with selected ligands.

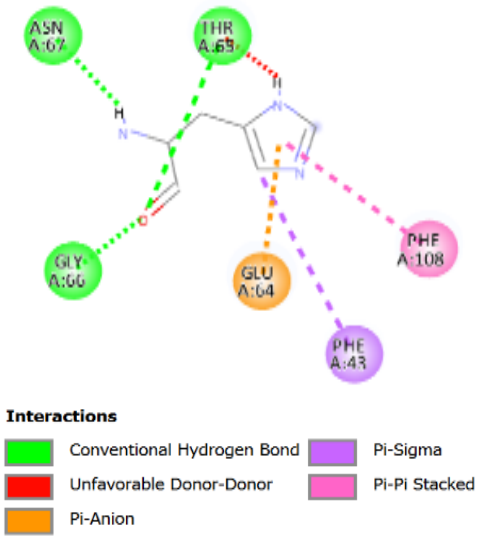
Ligands	Binding affinity
4uj1_108058_uff_E=243441013673.93	-13.6
4uj1_73078_uff_E=115950689.09	-12.2
4uj1_119058016_uff_E=1167.80	-10
4uj1_3086007_uff_E=1150.07	-9.5

Table 3. Docking score of 6E99 protein with selected ligands.

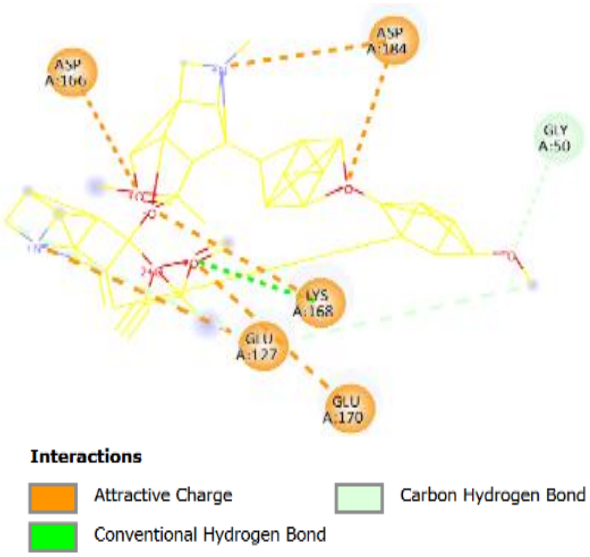
Ligands	Binding affinity
6e99_108058_uff_E=243441013673.93	-16.3
6e99_119058016_uff_E=1167.80	-10.5
6e99_442428_uff_E=919.77	-10.2
6e99_5280805_uff_E=825.99	-9.6
6e99_65064_uff_E=391.78	-9.2

Selected ligands **2D Structure**

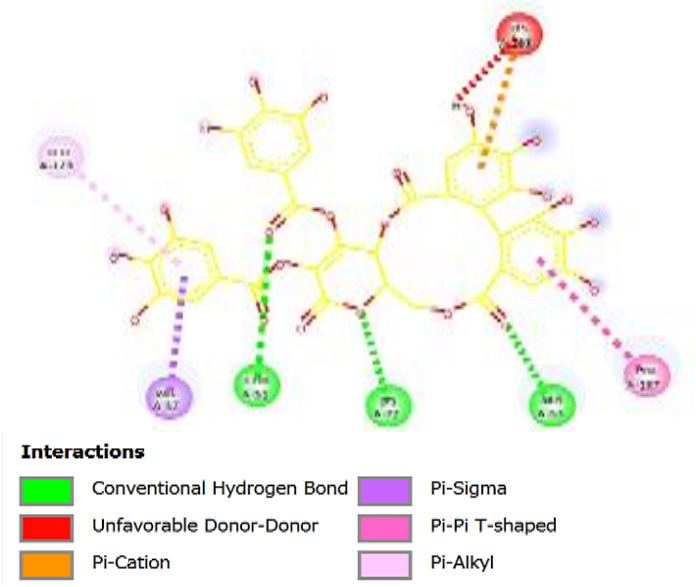
(a) 108058



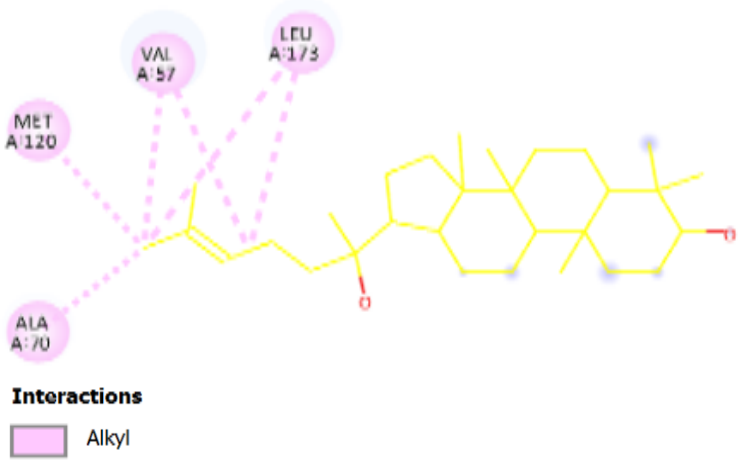
(b) 73078



(c) 119058016



(d) 3086007



(e) 11973122

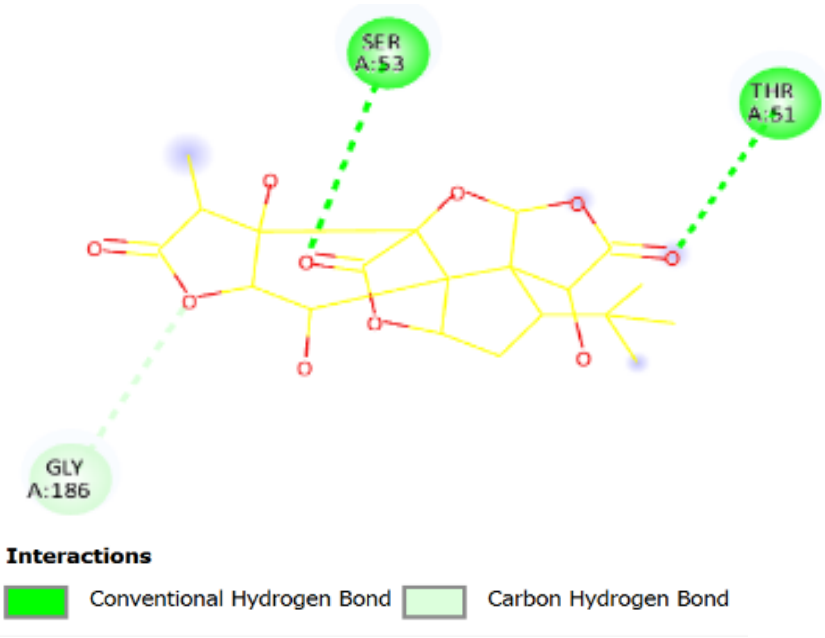
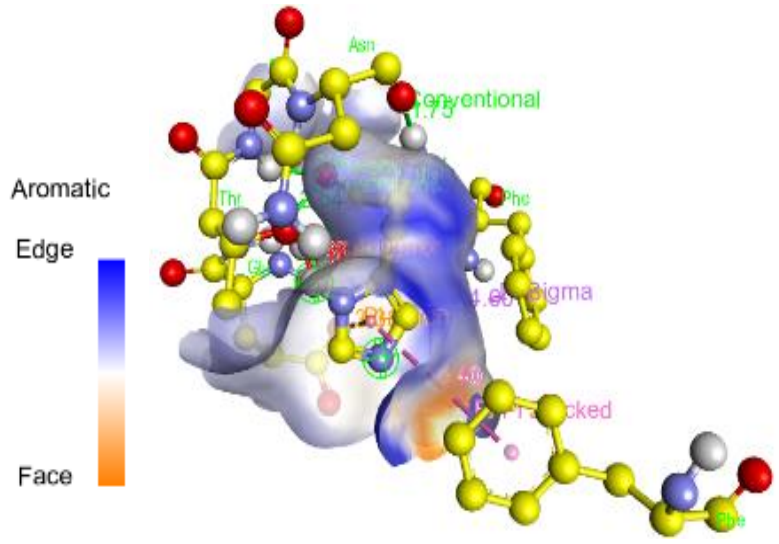


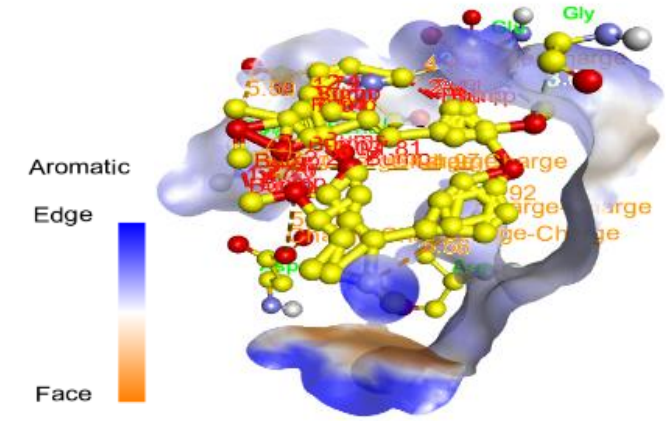
Figure 6. (a-e) 2D structure of the selected ligand of protein 4UJ1.

Selected ligands **3D Structure**

(a) 108058



(b) 73078



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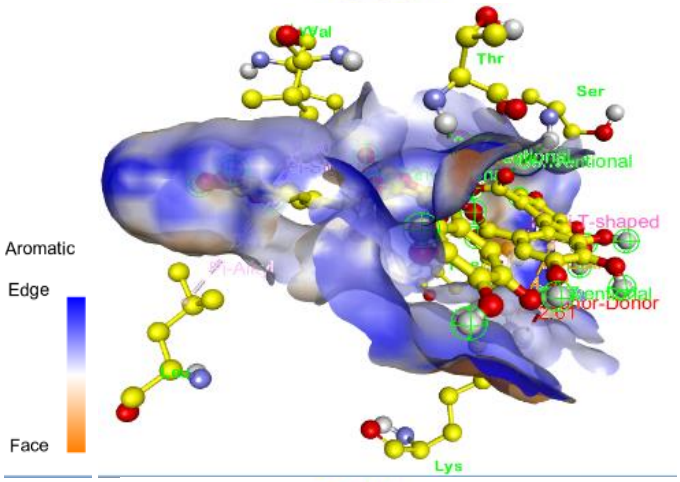

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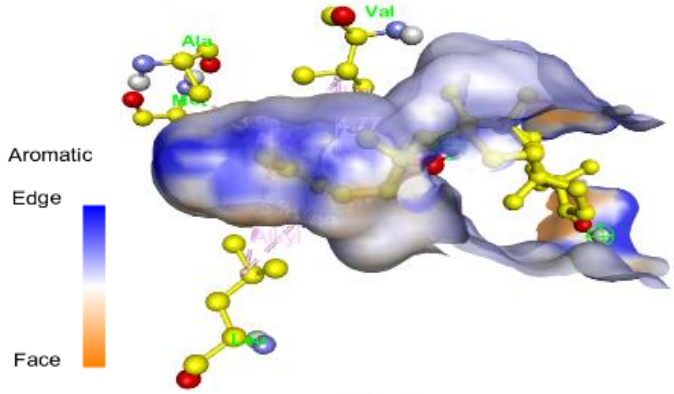


(e) 11973122

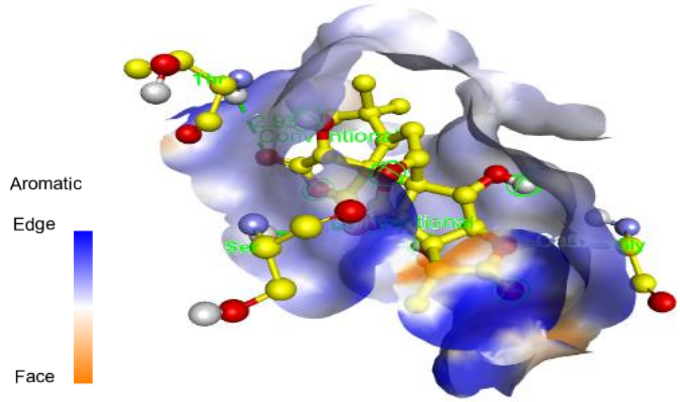
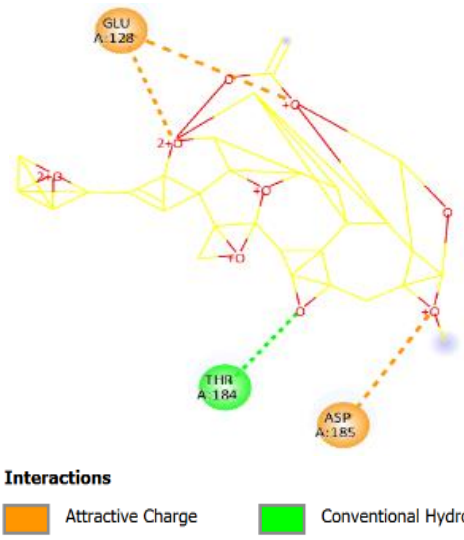


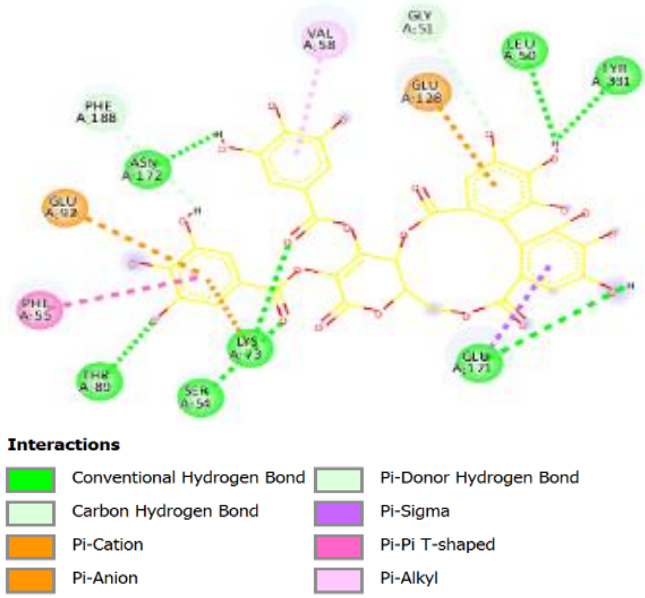
Figure 7. (a-e) 3D structure of the selected ligand of protein 4UJ1.

Selected ligands **2D structure**

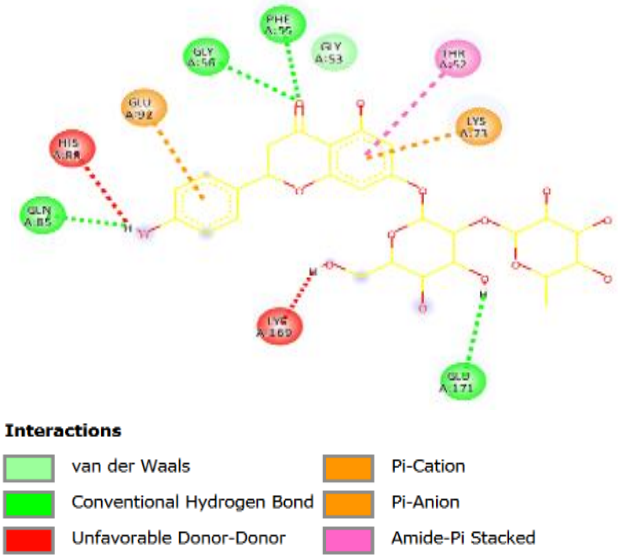
(a) 108058



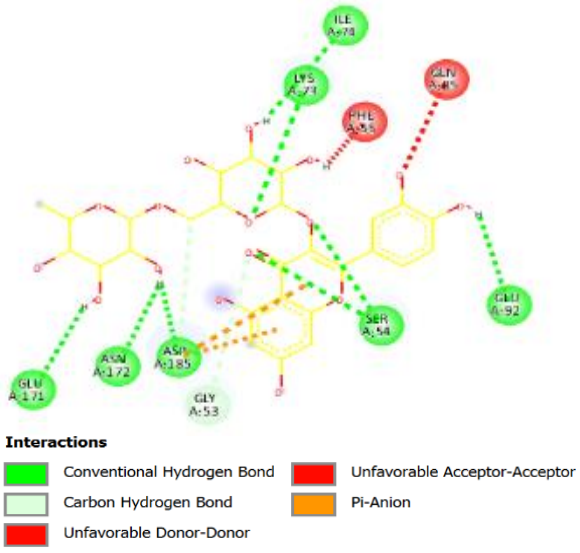
(b) 119058016



(c) 442428



(d) 5280805



(e) 65064

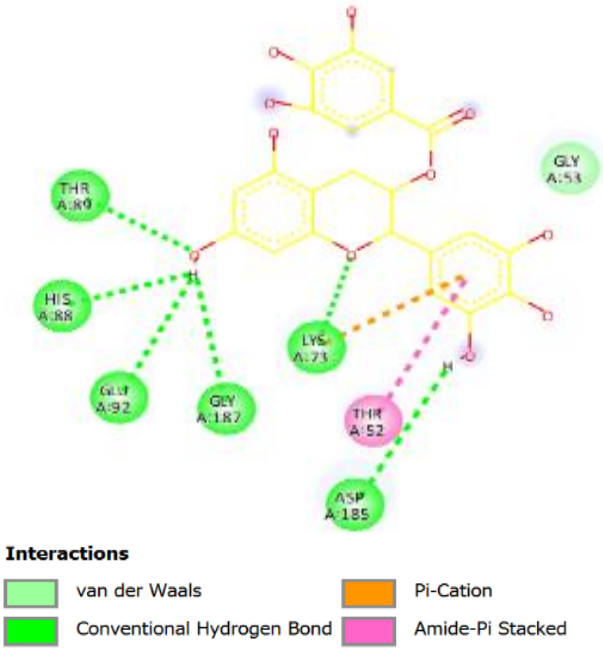
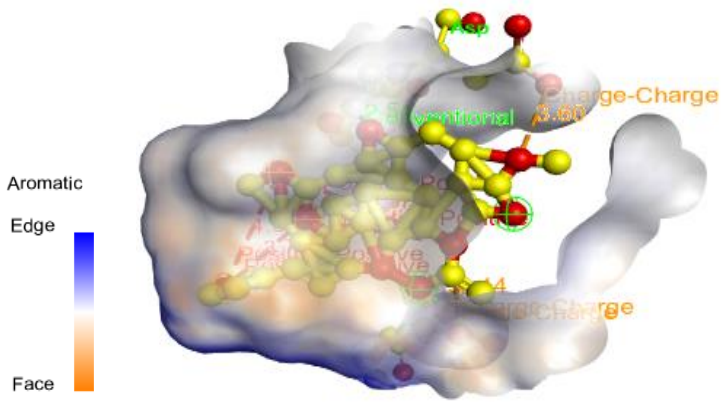


Figure 8. (a-e) 2D structure of selected ligand of protein 6E99.

Selected ligands **3D structure**

(a) 108058



(b) 119058016

(c) 442428

(d) 5280805

(e) 65064

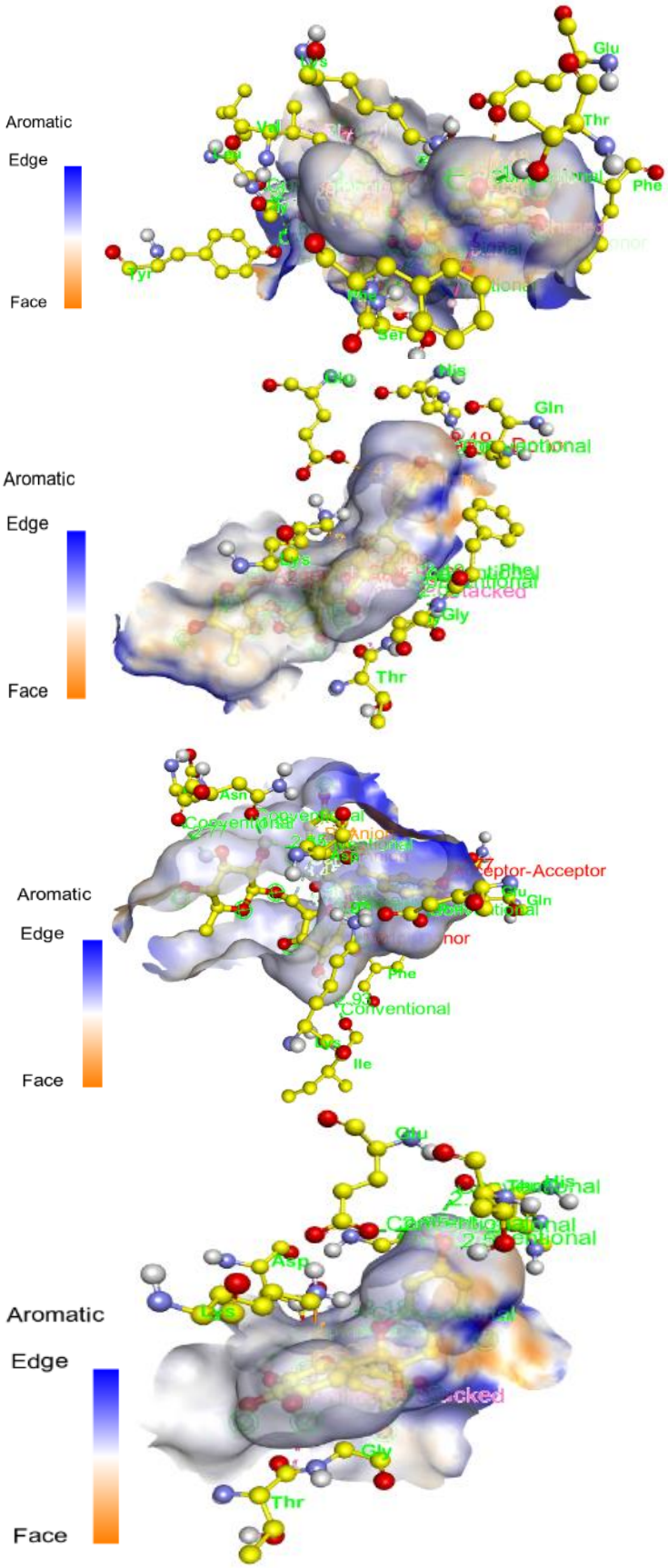


Figure 9. (a-e) 3D structure of selected ligand of protein 6E99.

Table 4. The canonical SMILES and PubChem ID of the top five ligands.

Ligands	PubChem ID	Canonical smiles
a. Nimbin	108058	CC1(CCC2(CCC3(C(=CCC4C3(CCC5C4(CCC(C5(C)C)O)C)C)C2C1)C)C(=O)O)C
b. Tetrandrine	73078	CC1=C2C(CC1C3=COC=C3)OC4C2(C(C5(C(C4OC(=O)C)C(C=CC5=O)(C)C(=O)OC)C)CC(=O)OC)C
c. Emblicanin A	119058016	C1=CC(=C(C=C1CCC(=O)C2=C(C=C(C(=C2O)C3C(C(C(C(O3)CO)O)O)O)O)O)O)O)O
d. Ginsenosides	3086007	C1C2C(C(=C(C(=O)O2)OC(=O)C3=CC(=C(C(=C3)O)O)O)OC(=O)C4=CC(=C(C(=C4)O)O)O)OC(=O)C5=CC(=C(C(=C5C6=C(C(=C(C=C6C(=O)O1)O)O)O)O)O)O)O
e. Ginkgolides	11973122	CC1C2C(CC3(C2(CC(=O)C4(C3CC=C5C4C=C(C(=O)C5(C)C)O)C)C)C)OC(CC1=O)C(C)(C)O

Table 5. Using SwissADME, properties of the Lipinski rule were obtained.

Ligands	Mol. wt.	MlogP	nHA	nHD
a. Nimbin	540.60 g/mol	2.04	9	0
b. Tetrandrine	622.75 g/mol	3.73	8	0
c. Emblicanin A	622.75 g/mol	3.73	8	0
d. Ginsenosides	444.73 g/mol	6	2	2
e. Ginkgolides	424.40 g/mol	0.06	10	3

Table 6. Physicochemical properties of the top five ligands.

Ligands	Formulae	Mol wt.	Rotatable bonds	Fraction Csp3	Molar refractivity	TPSA
a. Nimbin	C30H36O9	540.60 g/mol	8	0.60	138.81	118.34 Å²
b. Tetrandrine	C38H42N2O6	622.75 g/mol	4	0.37	186.07	61.86 Å²
c. Emblicanin A	C38H42N2O6	622.75 g/mol	4	0.37	186.07	61.86 Å²
d. Ginsenosides	C30H52O2	444.73 g/mol	4	0.93	138.72	40.46 Å²
e. Ginkgolides	C20H24O10	424.40 g/mol	1	0.85	93.29	148.82 Å²

Table 7. Pharmacokinetics of the top five ligands.

Ligands	GI absorption	BBB permeation	PGP substrate	CYP1A2 inhibitor	CYP2C19 inhibitor
a. Nimbin	High	No	No	No	No
b. Tetrandrine	High	No	No	No	No
c. Emblicanin A	High	No	No	No	No
d. Ginsenosides	Low	No	No	No	No
e. Ginkgolides	Low	No	Yes	No	No

Table 8. Drug-likeness of the top five ligands.

Ligands	Solubility (ESOL)	Bioavailability	PAINS	BRENK	Synthetic accessibility
a. Nimbin	Moderately soluble	0.55	0	2	6.54
b. Tetrandrine	Poorly soluble	0.55	0	0	7.01
c. Emblicanin A	Poorly soluble	0.55	0	0	7.01
d. Ginsenosides	Poorly soluble	0.55	0	1	5.98
e. Ginkgolides	soluble	0.55	0	1	6.38

Table 9. Screening of the top five ligands.

Ligands	Violation	Drug-likeness	GI absorption	Bioavailability score	PAINS alert
a. Nimbin	1	Yes	High	0.55	0
b. Tetrandrine	1	Yes	High	0.55	0
c. Emblicanin A	1	Yes	High	0.55	0
d. Ginsenosides	1	Yes	Low	0.55	0
e. Ginkgolides	0	Yes	Low	0.55	0

Table 10. Toxicity Prediction of the selected ligands.

Ligands	Predicted LD50	Predicted toxicity class	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
Nimbin	1000mg/kg	4	Inactive	Active	Active	Inactive	Inactive
Tetrandrine	1700mg/kg	4	Inactive	Active	Active	Active	Inactive
Emblicanin A	10000mg/kg	6	Inactive	Inactive	Inactive	Inactive	Inactive
Ginsenosides	2260mg/kg	5	Inactive	Inactive	Active	Inactive	Inactive
Ginkgolides	500mg/kg	4	Inactive	Inactive	Active	Inactive	Inactive

DISCUSSION

The historical aspect, tracing back to Egyptians and the evolution of the term “diabetes mellitus” by the Greek physician Aertaeus, provides a context for understanding the long-standing recognition and study of this condition. The prevalence of diabetes, affecting approximately 6% of the global population, underscores its widespread impact on health. Approximately 6% of people worldwide suffer from diabetes, demonstrating its pervasive effects on health.

The focus of the discussion is on how diabetes and obesity are related, with the word “diabesity” highlighting the close connection between type 2 diabetes and obesity. A contemporary perspective is brought to the discussion by the global growth in obesity rates, which are connected to several factors, such as sedentary lifestyles and dietary modifications.

Disruption of protein kinase A (PKA) signaling, particularly in Regulatory Subunit 2 B (R2B), is a key finding in the pathophysiology of diabetes. The association between obesity and this signaling system raises questions about the possible consequences of metabolic diseases and offers opportunities to find novel targets for obesity-related problems connected to obesity. The understanding of how genetic, environmental, and molecular factors interact highlights the intricacy of the etiology of obesity. The function of the brain in glucose homeostasis and gluconeogenesis provides insights into the complex processes that regulate blood glucose levels. To provide an overview of the rapidly changing field of diabetes treatment techniques, this study presents a prospective therapeutic approach that targets glucagon and inhibits CREB activity to prevent gluconeogenesis in persons with type 2 diabetes and obesity. The idea of pre-diabetes was introduced, highlighting the significance of blood glucose monitoring prior to crossing the barrier into diabetes. Treatment for obese people with diabetes is multimodal, encompassing lifestyle changes, medication, and, in severe cases, significant weight loss measures, such as bariatric surgery. This approach reflects the variety of strategies required for successful management. A further dimension to the discourse is the movement toward investigating natural components as substitutes for synthetic pharmaceuticals. With the historical background of the use of medicinal plants before the development of anti-diabetic medications, the interest in herbs and their antioxidant qualities points to a growing trend in the search for safer and more natural methods of managing diabetes.

To treat diabetes and obesity, secondary metabolites such as semaglutide and meglitinides were selected from the phytochemical components. Various plant compounds, such as polyphenols,

flavonoids, alkaloids, and terpenoids, have been reported to exert anti-hyperglycemic effects. After being downloaded in SDF format from PubChem (https://pubchem.ncbi.nlm.nih.gov/), the top 35 ligands were pharmacologically examined. Pharmacological and molecular docking analyses were performed on the ligands that exhibited the lowest binding qualities, namely Nimbin, Tetrandrine, Emblicanin A, Ginsenosides, and Ginkgolides, with binding scores of -13.6, -12.2, -10, -9.5, and -9.1, respectively (Figures 4-9 and Tables 2, 3). These interactions were visualized using Dassault Systems BIOVIA Discovery Studio. The drug's gastrointestinal absorption in humans, blood-brain permeation level, glycoprotein permeability, and solubility were all assessed during ADME testing. The BBB is a factor that determines a drug candidate's ability to pass through. Medicines cannot be synthesized without this knowledge. High gastrointestinal (GI) adsorption is required to enhance drug effectiveness. Oral drugs should have excellent gastrointestinal absorption and solubility for the maximum possible therapeutic effect. The top five ligands' canonical SMILES were obtained from PubChem and submitted for ADMET evaluation using the ADMETlab 2.0 website.

The phytocompounds Nimbin, Tetrandrine, Emblicanin A, Ginsenosides, and Ginkgolides appeared to have the best affinity for both protein targets (4UJ1 and 6E99), according to the current study's findings.

CONCLUSION

Considering the findings of this study, Nimbin had the best-binding affinity for 4UJ1 (-13.6) and 6E99 (-16.3). The investigation of the anti-hyperglycemic effects of plant secondary metabolites targeting the PKA/CREB pathway provides a promising avenue for future research and therapeutic development. The dynamic interplay between natural compounds and key signaling pathways offers a nuanced understanding of potential mechanisms, setting the stage for further exploration and innovation in the quest for effective and holistic approaches to diabetes management.

Acknowledgment

I express my gratitude to Ms. Susha Dinesh for her counsel and support and to BioNome for providing computational resources and assistance with scientific research services.

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