Journal of Advanced Biomedical Sciences

https://jabs.fums.ac.ir/
Online ISSN: 2783-1523

Journal of Advanced Biomedical Sciences

Fasa University of Medical Sciences

Identification of Alkaloid-Derived α-Glucosidase Inhibitors for Diabetes Management: An *In Silico* Approach

Mohsen Keshtmand, Morteza Sadeghi

Department of Biochemistry, Sa.C., Islamic Azad University, Sanandaj, Iran

Article Info

Article Type:
Original Article

Article history:
Received
29 Mar 2026
Received in revised form
13 Jul 2026
Accepted
14 Jul 2026
Published online
24 Jul 2026

Publisher
Fasa University of Medical Sciences

Abstract

Background & Objectives: Alkaloids constitute a structurally diverse class of naturally occurring compounds with a wide range of pharmacological activities. One of the principal mechanisms through which alkaloids may contribute to the management of diabetes mellitus (DM) is the inhibition of α-glucosidase. Despite their considerable therapeutic potential, the molecular interactions between alkaloids and α-glucosidase remain insufficiently characterized and warrant comprehensive investigation. Therefore, this study aimed to identify potential alkaloid-derived α-glucosidase inhibitors using an *in silico* approach for the management of DM.

Materials & Methods: An initial computational screening of 15 alkaloid ligands excluded cepharanthine because of predicted mutagenicity and immunotoxicity, whereas tetrandrine and fangchinoline were excluded because they failed to satisfy drug-likeness criteria. The remaining 12 compounds were subsequently subjected to molecular docking against α-glucosidase.

Results: Scopolamine exhibited the most favorable docking score (-6.91 kcal/mol), outperforming acarbose, the reference inhibitor (-6.87 kcal/mol). In the α-glucosidase and scopolamine complex, Arg699 and Glu301 participated in hydrogen bond and Pi anion interactions, respectively. Secondary structure analysis further revealed scopolamine induced conformational alterations in α-glucosidase, characterized by an increase in α-helix content and a reduction in β-sheet content, changes that were consistent with its predicted inhibitory activity.

Conclusion: These findings suggest that scopolamine is a promising candidate α-glucosidase inhibitor. Nevertheless, further *in vitro* and *in vivo* studies are required to validate its antidiabetic potential and determine its therapeutic value for controlling postprandial hyperglycemia in DM.

Keywords: Alkaloids, α-glucosidase inhibition, Diabetes mellitus, Scopolamine, *In silico*

Cite this article: Keshtmand M, Sadeghi M. Investigation of Treatment Adherence and Life Satisfaction in Psychiatric Patients Treated with Electroconvulsive Therapy: A cross-sectional study. J Adv Biomed Sci. 2026; 16(3): 251-264.
DOI: 10.18502/jabs.v16i3.21625

Introduction

Diabetes mellitus (DM) is an increasingly prevalent global health challenge, with the number of affected individuals projected to reach approximately 645 million by 2045 (1, 2). This metabolic disorder is characterized by persistent hyperglycemia and is associated with numerous debilitating complications, including neuropathy, nephropathy, and cardiovascular disease (3, 4). Consequently, identifying effective therapeutic strategies for DM has become a major research priority, particularly those aimed at controlling postprandial hyperglycemia. Among the most promising therapeutic targets are the intestinal carbohydrate digesting enzymes α-glucosidase

Corresponding Author: Morteza Sadeghi, Department of Biochemistry, Sa.C., Islamic Azad University, Sanandaj, Iran.
Email: mortezasadeghi@iau.ac.ir

CC BY NC

and α-amylase (5). α-glucosidase (EC 3.2.1.20), which is located in the brush border membrane of the small intestine, catalyzes the final stage of carbohydrate digestion by hydrolyzing α-1,4 and α-1,6 glycosidic linkages, thereby releasing glucose for subsequent absorption into the bloodstream (6, 7). Because this enzymatic process directly contributes to postprandial elevations in blood glucose levels, inhibition of α-glucosidase represents an effective therapeutic strategy for controlling postprandial hyperglycemia.

α-glucosidase inhibitors play a pivotal role in the management of DM by delaying carbohydrate digestion and reducing postprandial glucose excursions. Accordingly, the discovery and development of novel α-glucosidase inhibitors remain important objectives in antidiabetic drug research (8, 9). Several α-glucosidase inhibitors, including acarbose, voglibose, miglitol, deoxynojirimycin, metformin, and nateglinide (Figure 1), are currently used in clinical practice to improve glycemic control by inhibiting key digestive enzymes.

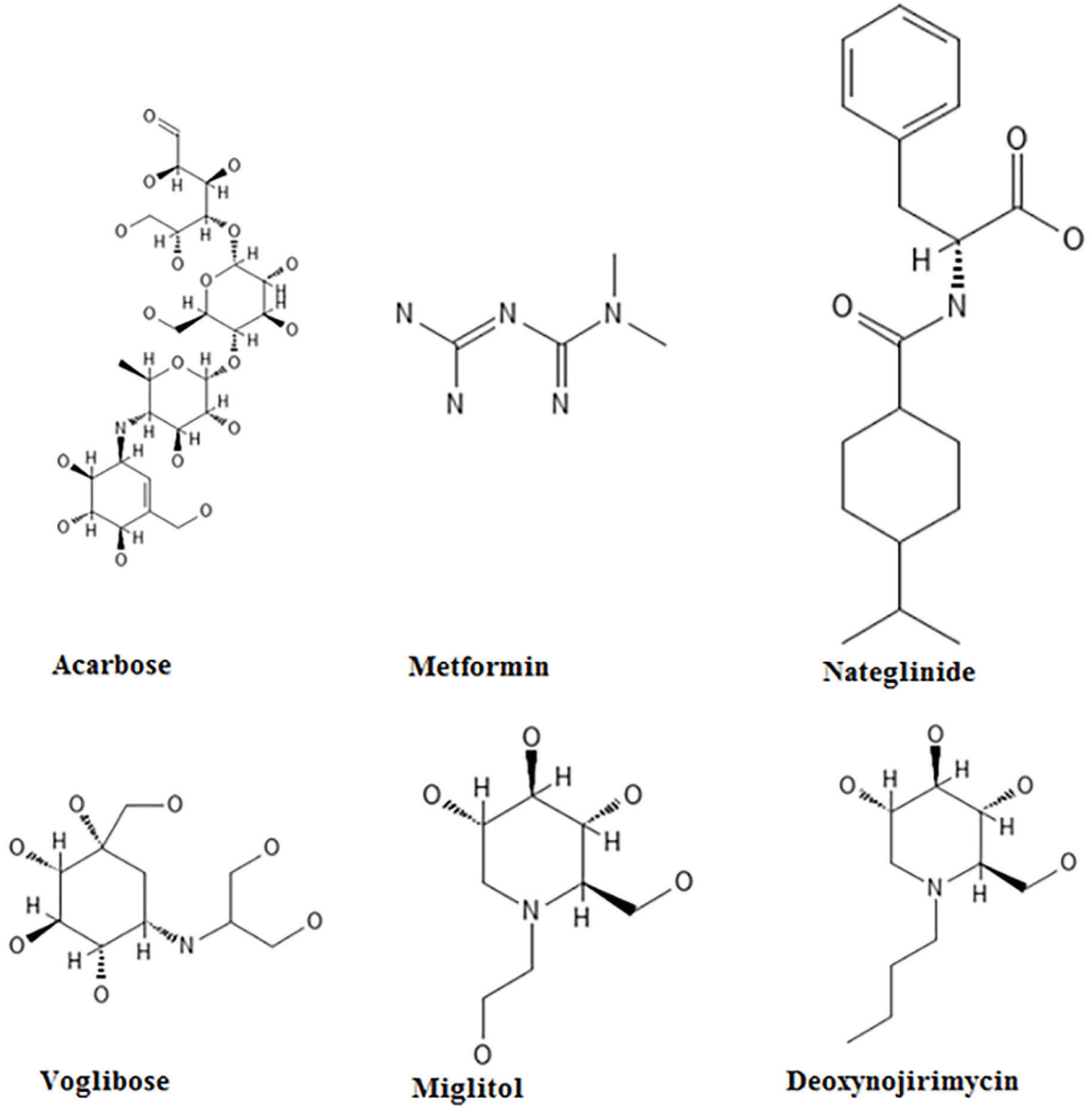


Figure 1. The chemical structures of the known α-glucosidase inhibitors (22).

However, their therapeutic use is often limited by adverse effects, including flatulence, hypoglycemia, abdominal discomfort, hepatotoxicity, and urinary tract complications (10-12). These limitations underscore the need to identify alternative α-glucosidase inhibitors with improved efficacy and safety profiles.

Natural products derived from fruits, vegetables, medicinal plants, and other dietary sources represent a rich reservoir of bioactive compounds with potential α-glucosidase inhibitory activity. Among these, alkaloids, together with terpenoids, phenolic acids, stilbenoids, and flavonoids, have attracted considerable attention because of their broad spectrum of biological and pharmacological activities (13, 14). Increasing evidence has highlighted the beneficial effects of alkaloids on human health, including antidiabetic, antioxidant, siderophore, attractant, and antiaging activities (15). Furthermore, several alkaloids have demonstrated potent α-glucosidase inhibitory activity. For example, berberine and jatrorrhizine have been reported to exhibit greater inhibitory potency than acarbose, a widely used reference inhibitor (16, 17). Likewise, Stefanello et al. (2014) demonstrated that caffeine effectively reduced blood glucose levels in diabetic rats, further supporting the therapeutic potential of alkaloids in diabetes management (18). Despite these encouraging findings, the molecular mechanisms underlying the interaction between alkaloids and α-glucosidase remain incompletely understood. Therefore, comprehensive *in silico* investigations are needed to characterize the binding modes and interaction profiles of diverse alkaloids with α-glucosidase.

Recent advances in computational drug discovery have established *in silico* methods as indispensable tools for identifying promising therapeutic candidates. These approaches facilitate high throughput virtual screening while reducing both the time and cost associated with conventional drug discovery and providing valuable computational data for rational drug design (19). Among these methods, molecular docking has emerged as a powerful technique for elucidating receptor ligand interactions and predicting binding affinities. When integrated with experimental investigations, computational approaches provide a more comprehensive understanding of the molecular mechanisms governing receptor ligand interactions (20, 21). Building on these advances, the present study aimed to systematically evaluate the α-glucosidase inhibitory potential of selected alkaloid compounds. Specifically, molecular docking was employed to predict their binding affinities, expressed as docking scores, and to characterize their interactions with the α-glucosidase active site.

Materials and Methods

Drug-Likeness Evaluation

The potential of the selected alkaloid compounds (Figure 2) as viable α-glucosidase inhibitors was systematically assessed by evaluating their drug-likeness properties. This analysis was designed to predict the compounds' pharmacokinetic behavior and oral suitability in accordance with established drug-likeness criteria (23). Key molecular descriptors, including molecular weight (MW), lipophilicity (logP), hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), and molar refractivity (MR), were calculated to determine compliance with Lipinski's Rule of Five and related guidelines. These physicochemical parameters were obtained using the SwissADME web server (http://www.swissadme.ch/index.php) (24) and cross-checked against the PubChem database (http://pubchem.ncbi.nlm.nih.gov). This preliminary screening helped ensure that the compounds possessed favorable pharmacokinetic characteristics and, therefore, had potential as orally bioavailable drug candidates.

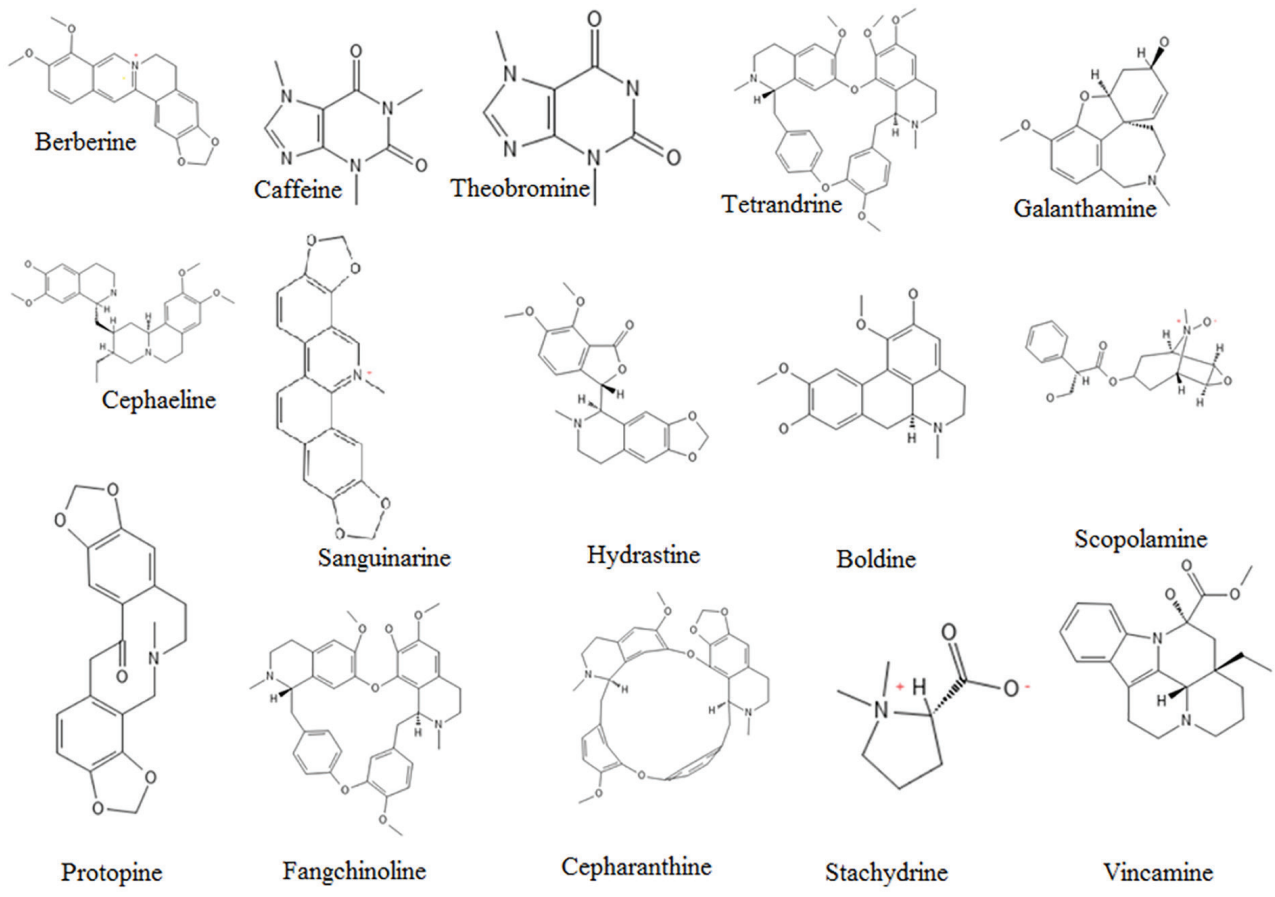


Figure 2. Chemical structure of alkaloids.

Toxicological Profile Prediction

In parallel, the toxicological properties of the selected alkaloids were rigorously predicted to identify potential safety concerns at an early stage of drug discovery. Toxicity evaluation is a critical step in determining a compound's suitability for therapeutic development. Potential adverse effects, including hepatotoxicity, mutagenicity, carcinogenicity, cytotoxicity, and immunotoxicity, were predicted computationally using the ProTox-II server (https://tox.charite.de/protox_II/) (25). In addition, each compound was assigned an overall toxicity class using Toxtree software, version 2.5.4 (26). This integrated predictive approach provided a comprehensive overview of the safety profiles of the alkaloid candidates and supported their prioritization for further biological and pharmacological investigation.

Molecular docking

To elucidate compound enzyme interaction modes, molecular docking was performed using AutoDock Tools 4.2.6 (27). The crystal structure of α-glucosidase (PDB ID: 3W38, 2.79 Å resolution) was retrieved from the RCSB Protein Data Bank (https://www.rcsb.org/structure/3W38). The compound structures, alkaloid sources, and PubChem IDs were obtained from the PubChem Compound database (https://pubchem.ncbi.nlm.nih.gov/) (Table 1). Energy minimization of α-glucosidase and all alkaloid compounds was carried out in UCSF Chimera (28), which was also used for charge assignment, water removal, polar hydrogen addition, and the assignment of Kollman and Gasteiger charges. A docking

Table 1. Properties some of important alkaloids in natural sources.

S.No	Alkaloids	Source	PubChem ID
1	Berberine	*Stephania tetrandra*	2353
2	Caffeine	*Camellia sinensis*	2519
3	Theobromine	*Camellia sinensis*	5429
4	Tetrandrine	*Cyclea barbata*	73078
5	Cephaeline	*Alangium salviifolium*	442195
6	Sanguinarine	*Glaucium squamigerum*	5154
7	Hydrastine	*Berberis aquifolium*	197835
8	Boldine	*Neolitsea konishii*	10154
9	Galanthamine	*Crinum moorei*	9651
10	Protopine	*Corydalis solida*	4970
11	Scopolamine	*Duboisia leichhardtii*	5184
12	Fangchinoline	*Stephania hernandifolia*	73481
13	Cepharanthine	*Stephania cephalantha*	10206
14	Stachydrine	*Achillea setacea*	115244
15	Vincamine	*Vinca difformis*	15376

grid box was defined around the active site, encompassing the mapped α-glucosidase residues, with dimensions of 78 × 78 × 78 Å and centered at coordinates x = -14.33, y = -45.21, and z = 0.337 Å. The Lamarckian genetic algorithm was used for docking with the following parameters: 17,000 generations, 1,900,000 evaluations, 1,000 docking runs, and simulated annealing parameters of 0.3 Å/step and 6°/step. Post docking analysis of ligand 3W38 complex interactions was performed using BIOVIA Discovery Studio (DS) software (29, 30).

Evaluation of protein secondary structure

The 3D coordinate of 3W38 was retrieved from the Protein Data Bank for structural analysis. Initial preparation and local optimization of the structure were performed in UCSF Chimera v1.7. Energy minimization was carried out using the conjugate gradient algorithm together with the GROMOS 53A6 force field to relieve steric clashes and reduce local strain before downstream analysis. Secondary structure composition and architecture were assessed using the VADAR v1.8 web server (http://redpoll.pharmacy.ualberta.ca/vadar) (31), which provides residue level assignments of α helices, β sheets, β turns, and coils, as well as summary statistics relevant to secondary structure content. Structural inspection and presentation quality molecular graphics were generated with Discovery Studio v1.9. Together, these procedures yielded a refined model and a quantitative description of the α-glucosidase secondary structure elements for subsequent interpretation and discussion.

Results

***In Silico* Toxicity Assessment and Drug-likeness Evaluation**

The initial screening of potential α-glucosidase inhibitors began with a rigorous *in silico* evaluation of the selected ligands' toxicological profiles and drug-likeness properties. This multifaceted computational strategy is essential in the early stages of drug discovery because it enables the prioritization of compounds with favorable safety and pharmacological characteristics and reduces the likelihood of failure in subsequent *in vitro* and *in vivo* studies.

***In Silico* toxicity assessment and drug-likeness evaluation of ligands**

All 15 selected ligands underwent comprehensive *in silico* toxicity prediction, and the findings are summarized in Table 2.

Table 2. Predicted Toxicological Profiles and Classification of Compounds; (A positive sign (+) denotes predicted toxicity, while a negative sign (−) indicates predicted non-toxicity N.T; no toxic, T; toxic).

Compound	Hepatotoxicity	Mutagenicity	Immunotoxicity	Carcinogenicity	Toxicity Class	Status
Berberine	−	−	−	−	VI	NT
Caffeine	−	−	−	−	V	NT
Theobromine	−	−	−	−	V	NT
Tetrandrine	−	−	−	−	VI	NT
Cephaeline	−	−	−	−	VI	NT
Sanguinarine	−	−	−	−	VI	NT
Hydrastine	−	−	−	−	V	NT
Boldine	−	−	−	−	VI	NT
Galanthamine	−	−	−	−	V	NT
Protopine	−	−	−	−	VI	NT
Scopolamine	−	−	−	−	V	NT
Fangchinoline	−	−	−	−	IV	NT
Cepharanthine	−	+	+	−	III	T
Stachydrine	−	−	−	−	V	NT
Vincamine	−	−	−	−	IV	NT

Because the absence of significant toxicity is a fundamental prerequisite for any prospective drug candidate, comparative toxicological profiling was performed to identify and exclude compounds with unfavorable safety attributes. The toxicity of the tested ligands was categorized into six classes according to established guidelines: Class I, highly toxic substances; Classes II and III, compounds exhibiting general toxicity; Class IV, low toxicity; and Classes V and VI, non-toxic or safe compounds (32). Among the 15 compounds assessed, Cepharanthine was predicted to have mutagenic and immunotoxic properties. This unfavorable toxicological profile led to its exclusion from further analysis, underscoring the value of early stage *in silico* screening for eliminating problematic compounds. The remaining 14 compounds were predicted to be non-toxic and, therefore, were considered for subsequent evaluation of drug-likeness criteria.

These 14 non-toxic compounds were then evaluated according to drug-likeness criteria, including Lipinski's Rule of Five, as shown in Table 3. The analysis indicated that Tetrandrine and Fangchinoline failed to satisfy specific parameters, such as molecular weight greater than 500 Da and elevated logP values. Consequently, these two compounds were excluded from further analysis. In total, 12 ligands met both the toxicological and drug-likeness criteria and were therefore selected for further investigation as potential α-glucosidase inhibitors.

Following the toxicity assessment, the 14 identified non-toxic compounds were systematically evaluated for their adherence to key drug-likeness criteria, as extensively detailed in Table 3. These parameters, predominantly derived from Lipinski's "Rule of Five" and other established guidelines, are instrumental in predicting oral bioavailability and membrane permeability, thereby enabling the early exclusion of ligands unlikely to progress as viable drug candidates. It is imperative to acknowledge that while compliance with these drug-likeness parameters is highly indicative of favorable ADME (Absorption, Distribution, Metabolism, and Excretion) properties, it does not unequivocally guarantee a compound's ultimate suitability as a drug. Rather, these criteria serve as powerful predictive tools for enriching the compound pool with promising candidates and efficiently eliminating suboptimal ligands at the preclinical evaluation

Table 3. Comprehensive Drug-Likeness Evaluation of Ligands Utilizing Lipinski's Rule of Five Criteria, Including key Physicochemical Properties.

Compound	Hydrogen bond donors (≤ 5)	Hydrogen bond acceptors (≤ 10)	Molecular mass (< 500)	Log*p* (<5)	Molar Refractivity (35–150)	Lipinski filter
Berberine	0	4	336.36	3.62	94.87	Yes; 0 violation
Caffeine	0	3	194.19	-0.07	52.04	Yes; 0 violation
Theobromine	1	3	180.16	-0.78	47.14	Yes; 0 violation
Tetrandrine	0	8	622.75	6.66	186.07	No; 2 violation
Cephaeline	2	6	466.61	4.41	142.58	Yes; 0 violation
Sanguinarine	0	4	332.33	4.45	94.68	Yes; 0 violation
Hydrastine	0	7	383.39	2.74	103.38	Yes; 0 violation
Boldine	2	5	327.37	2.72	96.00	Yes; 0 violation
Galanthamine	1	4	287.35	1.84	84.05	Yes; 0 violation
Protopine	0	6	353.37	2.79	97.49	Yes; 0 violation
Scopolamine	1	5	303.35	0.98	83.48	Yes; 0 violation
Fangchinoline	1	8	608.72	6.34	181.60	No; 2 violation
Stachydrine	0	2	143.18	0.40	41.35	Yes; 0 violation
Vincamine	1	4	354.44	2.86	103.74	Yes; 0 violation

stage. The comprehensive evaluation indicated that, with the notable exceptions of Tetrandrine and Fangchinoline, all selected alkaloids successfully met the defined drug-likeness criteria. These two compounds were identified as outliers due to non-compliance with specific parameters (e.g., molecular weight exceeding 500 Da, or high logP values), which are critical for oral drug candidates. Consequently, based on both favorable toxicological profiles and satisfactory drug-likeness, a total of 12 ligands were identified as suitable candidates for further in-depth investigation as potential α-glucosidase inhibitors.

Molecular Docking

Molecular docking was performed on the 12 selected alkaloids targeting the active site of α-glucosidase, which comprises residues Arg676, Arg699, Asp666, Ile672, and Thr662. Acarbose was used as the reference standard. The docking results showed that scopolamine exhibited the highest binding affinity among the tested ligands, with a minimum docking energy of -6.91 kcal/mol, which was slightly lower and thus more favorable than that of acarbose (-6.87 kcal/mol) (Table 4).

Molecular docking is a well-established computational strategy in drug design that enables the prediction of optimal binding modes and binding affinities between a ligand and its receptor (33, 34). Its primary objective is to identify low energy conformations of ligand receptor complexes and to determine the specific amino acid residues of the enzyme that interact with the ligand atoms. In this study, a panel of 12 selected alkaloid compounds was subjected to molecular docking analysis targeting the active site of α-glucosidase. Based on previous structural and mechanistic studies, the active site of α-glucosidase is known to include key residues such as Arg676, Arg699, Asp666, Ile672, and Thr662. Docking energy was used as the principal evaluation criterion, with acarbose serving as the reference standard because of its established inhibitory activity against α-glucosidase. The docking analysis revealed that scopolamine had a stronger predicted binding affinity for α-glucosidase than acarbose. Specifically, the scopolamine α-glucosidase complex yielded a minimum docking energy of -6.91 kcal/mol, which was slightly more favorable than the -6.87 kcal/mol observed for the acarbose α-glucosidase complex (Table 4).

Table 4. Docking score of alkaloids and reference drug (acarbose). Molecular docking scores for the selected alkaloids were comparatively analyzed against those obtained for the acarbose, to assess their potential binding affinities and efficacy.

Alkaloids	Docking energy (Kcal/mol)	Van der waals	Hydrogen-bond	Electrostatics
Scopolamine	-6.91	-4.27	-1.73	-0.91
Acarbose (Ref)	-6.87	-4.91	-1.43	-0.53
Caffeine	-6.11	-5.14	-0.82	-0.14
Sanguinarine	-5.91	-4.18	-1.15	-0.57
Theobromine	-5.88	-4.24	-1.26	-0.38
Berberine	-5.72	-3.91	-1.79	-0.02
Hydrastine	-5.52	-3.45	-1.41	-0.66
Boldine	-5.43	-4.26	-1.14	-0.03
Cephaeline	-5.34	-3.88	-1.79	-0.33
Vincamine	-5.25	-3.59	-1.26	-0.40
Protopine	-4.86	-3.27	-1.17	-0.44
Galanthamine	-4.71	-3.31	-1.11	-0.29
Stachydrine	-4.36	-3.18	-1.12	-0.06

Detailed analysis of the scopolamine α-glucosidase docked complex (Figure 3A and C) revealed the key intermolecular interactions responsible for stabilizing the complex. Conventional hydrogen bonds were formed between scopolamine and residues Arg699 and Arg676. In addition, Pi anion interactions were identified with Glu301, Asp666, and Arg670. The complex was further stabilized by seven van der Waals interactions. By comparison, the acarbose α-glucosidase docked complex (Figure 3B and D) exhibited a distinct interaction profile. Pi alkyl interactions were observed with His112, Phe159, and Phe178, whereas conventional hydrogen bonds were formed with Gln279, Glu277, His280, Asp307, Glu411, Asp215, and Asp315. In addition, the complex was stabilized by seven van der Waals interactions. Overall, the molecular interaction analysis demonstrated that the scopolamine α-glucosidase complex exhibited a highly favorable interaction pattern characterized by multiple conventional hydrogen bonds, Pi anion interactions, and extensive van der Waals contacts (Figure 4). These findings, together with its more favorable docking energy, suggest that scopolamine has a stronger predicted binding affinity for α-glucosidase than acarbose.

Analysis of secondary structure changes upon ligand binding

The impact of Scopolamine binding on the secondary structure of α-glucosidase was analyzed using the VADAR server (Table 5). Upon complexation, the α-helical content of the enzyme increased from 10.27% (free state) to 18.91% (bound state). Conversely, the β-sheet content decreased significantly from 39.83% in the free enzyme to 20.46% in the Scopolamine-bound complex.

The effect of scopolamine binding on the secondary structure of α-glucosidase was evaluated using the VADAR web server, a validated bioinformatics platform for comprehensive protein secondary structure analysis (35). This *in silico* analysis enabled a detailed comparison of the structural composition of the free enzyme with that of the scopolamine bound complex, thereby providing insight into the conformational changes induced by ligand binding.

As summarized in Table 5, scopolamine binding produced substantial alterations in the secondary structure of α-glucosidase. Specifically, the α-helical content increased from 10.27% in the unbound enzyme to 18.91% following complex formation. In contrast,

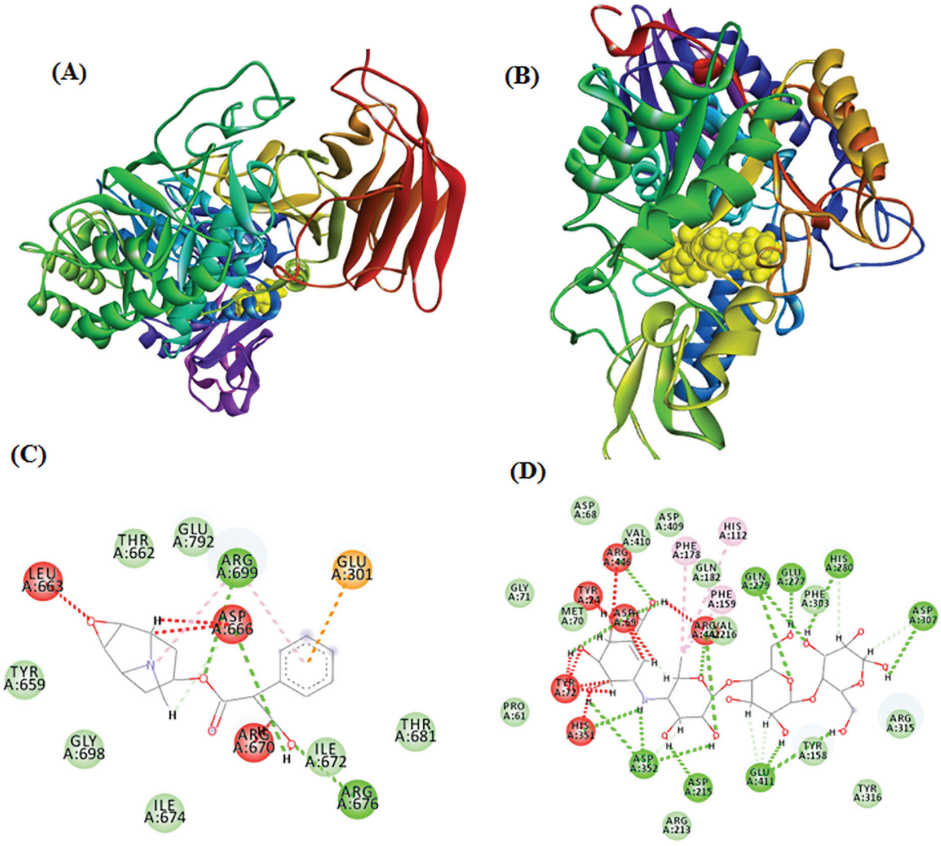


Figure 3. Molecular docking analysis of scopolamine and acarbose with α-glucosidase. (A) Overall docked conformation of the scopolamine α-glucosidase complex, illustrating the predicted binding pose within the active site. (B) Overall docked conformation of the acarbose α-glucosidase complex, illustrating the predicted binding pose within the active site. (C) Two dimensional representation of the key interactions between scopolamine and residues within the α-glucosidase active site. (D) Two dimensional representation of the key interactions between acarbose and residues within the α-glucosidase active site.

the β-sheet content decreased markedly from 39.83% in the free enzyme to 20.46% in the scopolamine bound complex.

These findings indicate that scopolamine binding induces pronounced conformational rearrangements within α-glucosidase, promoting the formation of α-helical structures while reducing β-sheet content. Ligand induced conformational changes of this nature are known to influence enzymatic function by altering the spatial organization of catalytic residues and modulating the overall structural dynamics of the protein. The observed structural reorganization is consistent with the strong binding affinity predicted by the molecular docking analysis, in which the scopolamine α-glucosidase complex exhibited a binding energy of -6.91 kcal/mol (Table 4), indicative of a stable enzyme ligand complex.

The marked reduction in β-sheet content, together with the concomitant increase in α-helical structure, suggests that scopolamine binding may shift α-glucosidase toward a less catalytically favorable conformation. Such conformational remodeling could impair substrate recognition or catalytic efficiency by modifying the architecture and dynamics of the active site. Accordingly, these structural changes provide a plausible molecular basis for the predicted inhibitory activity of scopolamine.

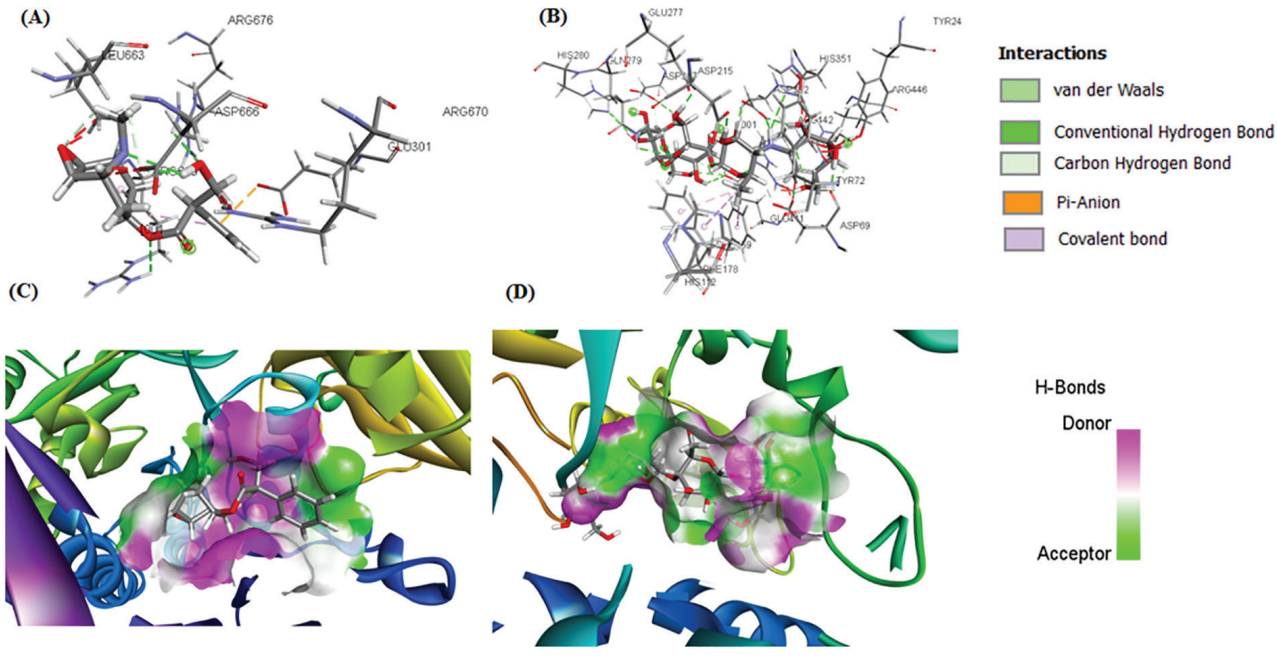


Figure 4. (A) 3D visualization of the scopolamine-α-glucosidase complex, highlighting spatial orientation and proximity of interacting residues. **(B)** 3D visualization of the acarbose-α-glucosidase complex, highlighting spatial orientation and proximity of interacting residues. **(C)** Detailed representation of hydrogen bond interactions within the scopolamine-α-glucosidase complex. **(D)** Detailed representation of hydrogen bond interactions within the acarbose-α-glucosidase complex.

Table 5. Changes in the secondary structure content of α-glucosidase upon scopolamine binding.

Structure	α-helix (%)	β-sheet (%)	B-turn (%)	Random coil (%)
Free α-glucosidase	10.27	39.83	19.11	30.79
scopolamine/α-glucosidase complex	18.91	20.46	20.14	40.49

By stabilizing a conformation that is less conducive to catalysis, scopolamine may reduce the enzymatic hydrolysis of dietary carbohydrates in the small intestine, thereby slowing glucose release into the circulation and contributing to the control of postprandial hyperglycemia.

Discussion

The rigorous *in silico* evaluation of toxicological profiles and drug-likeness is essential for prioritizing compounds with favorable safety and pharmacological characteristics at an early stage of drug discovery. The exclusion of cepharanthine on the basis of predicted mutagenic and immunotoxic properties highlights the value of this approach in eliminating problematic compounds before proceeding to costly *in vitro* and *in vivo* investigations. Likewise, the application of Lipinski's Rule of Five led to the exclusion of tetrandrine and fangchinoline, both of which showed limited potential for oral bioavailability because of their high molecular weight and logP values. As a result, the compound pool was efficiently narrowed to 12 promising candidates.

The molecular docking results indicate that scopolamine exhibits a stronger predicted binding affinity for α-glucosidase than the

reference drug acarbose, as reflected by its more favorable docking energy of -6.91 kcal/mol compared with -6.87 kcal/mol for acarbose. In addition, the scopolamine complex displayed a greater overall number of favorable interactions, including conventional hydrogen bonds, Pi anion interactions, and van der Waals forces, than the acarbose complex. Collectively, these interactions suggest a more stable and tighter binding mode for scopolamine within the active site.

Although acarbose forms a greater number of hydrogen bonds than scopolamine, its comparatively lower binding affinity may be explained by the entropic penalty associated with its larger and more flexible structure, which can hinder the adoption of an optimal rigid conformation within the enzyme active site. Moreover, the contribution of hydrophobic interactions and Pi anion interactions, which were more pronounced in scopolamine, may outweigh the electrostatic contribution of the multiple hydrogen bonds observed in acarbose.

The secondary structure analysis provides additional mechanistic insight into the inhibitory potential of scopolamine. The substantial increase in α-helical content, together with the marked reduction in β-sheet content after ligand binding, indicates pronounced conformational rearrangement of the enzyme. These structural changes are likely a consequence of scopolamine's strong binding affinity, which may alter the enzyme's conformational dynamics on a larger scale. Such ligand induced conformational transitions can modulate enzyme activity by changing the spatial arrangement of amino acid residues in the active site or by affecting overall protein flexibility. In this context, the observed decline in β-sheet content and increase in α-helical content suggest that scopolamine binding may shift α-glucosidase toward a less catalytically efficient conformation. Accordingly, this structural explanation supports the proposed mechanism by which scopolamine may impede the catabolism of complex carbohydrates in the small intestine, thereby reducing the rapid release of glucose into the bloodstream. This mechanism further supports the potential of scopolamine as an effective agent for managing postprandial hyperglycemia.

Limitations of the Study

Although this study provides important insights into the potential inhibitory mechanism of the identified alkaloids, several limitations should be acknowledged. First, the analysis relied primarily on static molecular docking and predictive structural modeling using VADAR, without assessing complex stability through molecular dynamics simulations or verifying conformational changes experimentally by circular dichroism spectroscopy. Second, the absence of secondary structure data for the acarbose enzyme complex limits our ability to determine the structural specificity of the scopolamine induced changes in direct comparison with acarbose. Finally, the lack of *in vitro* enzymatic assays means that the reported inhibitory activities remain computational predictions. Therefore, future studies should incorporate molecular dynamics simulations and experimental validation to confirm the efficacy and structural specificity of the identified alkaloids.

Conclusion

This study systematically examined a panel of alkaloid compounds by integrating rigorous *in silico* analyses to identify and characterize novel α-glucosidase inhibitors. The initial toxicological and drug-likeness assessments served as an effective filtering step, successfully excluding compounds with unfavorable safety profiles, such as cepharanthine, as well as compounds with suboptimal pharmacokinetic properties, such as tetrandrine and fangchinoline. This process narrowed the candidate pool to 12 promising ligands. Molecular docking provided

compelling evidence that scopolamine has a superior binding affinity for α-glucosidase, as demonstrated by its favorable docking energy and diverse intermolecular interactions within the enzyme active site. Mechanistically, the secondary structure analysis showed that scopolamine binding induces substantial conformational rearrangements in α-glucosidase, characterized by increased α-helical content and a concomitant decrease in β-sheet content. These structural changes are likely central to its inhibitory effect, potentially rendering the enzyme less catalytically efficient. Overall, this study identifies scopolamine as a highly promising α-glucosidase inhibitor with favorable drug-like properties and strong predicted binding affinity. The findings not only support the utility of integrated computational approaches in drug discovery but also provide a strong rationale for further preclinical and clinical evaluation of scopolamine as a potential therapeutic agent for managing postprandial hyperglycemia and slowing the progression of DM. Future research should focus on *in vivo* efficacy, long-term toxicity, and pharmacokinetic profiling to more fully define scopolamine's therapeutic potential.

Acknowledgments

This work is based upon research funded by Iran National Science Foundation (INSF) under project No40405653.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Funding

No external funding was received for this study.

Ethical Considerations

This study received ethical approval from the Iran National Science Foundation (INSF) under project No. 40405653.

Code of Ethics

No40405653

Author's Contribution

Mohsen Keshtmand: Reviewed and edited the manuscript. Morteza Sadeghi: Formal analysis, Supervision, Writing original draft, Methodology, Data curation, Writing-reviewing & editing.

References

1 Zhou B, Rayner AW, Gregg EW, Sheffer KE, Carrillo-Larco RM, Bennett JE, et al. Worldwide trends in diabetes prevalence and treatment from 1990 to 2022: a pooled analysis of 1108 population-representative studies with 141 million participants. Lancet. 2024;404(10467):2077-93.

2 Hoda F, Arshad M, Zayed S, Khan MA, Habib MA, Najmi AK. Prevalence of Diabetic Kidney Disease in Indian Type 2 Diabetes Mellitus Patients: A Meta-Analysis. Diabetes Metab Syndr.: Clin Res Rev. 2025:103267.

3 Milan K, Megha B, Ramkumar K. Role of inflammasomes in diabetes mellitus: mechanisms, complications, and therapeutic potential. Mol Biol Rep. 2025;52(1):621.

4 Giannakogeorgou A, Roden M, Pafili K. Diabetes mellitus as a multisystem disease: understanding subtypes, complications, and the link with steatotic liver diseases in humans. Hormones. 2025:1-20.

5 Roney M, Huq AM, Rullah K, Zamri NB, Mohd Aluwi MFF. Curcumin, a bioactive compound of Turmeric (Curcuma longa) and its derivatives as α-amylase and α-glucosidase inhibitors. CBB. 2025;83(1):53-71.

6 Abdelgawad MA, Musa A, Mostafa EM, Shaker ME, Nayl A, Selim S, et al. Synthesis and characterization of novel pyrazoline derivatives as dual α-amylase/α-glucosidase inhibitors: molecular modeling and kinetic study. J Mol Struct. 2025;1339:142350.

7 Jha R, Goyal K, Mehan S, Singh G. Dual α-amylase and α-glucosidase inhibitors: recent progress from natural and synthetic resources. Bioorg Chem. 2025:108762.

8 Tavera-Hernández R, Jiménez-Estrada M, Alvarado-Sansininea JJ, Huerta-Reyes M. Chia (salvia hispanica L.), a pre-hispanic food in the treatment of diabetes mellitus: hypoglycemic, antioxidant, anti-inflammatory, and inhibitory properties of α-glucosidase and α-amylase, and in the

prevention of cardiovascular disease. Molecules. 2023;28(24):8069.
9 Riyaphan J, Pham D-C, Leong MK, Weng C-F. In silico approaches to identify polyphenol compounds as α-glucosidase and α-amylase inhibitors against type-II diabetes. Biomolecules. 2021;11(12):1877.
10 Oyewusi HA, Wu Y-S, Safi SZ, Wahab RA, Hatta MHM, Batumalaie K. Molecular dynamics simulations reveal the inhibitory mechanism of Withanolide A against α-glucosidase and α-amylase. J Biomol Struct Dyn. 2023;41(13):6203-18.
11 Kaur N, Kumar V, Nayak SK, Wadhwa P, Kaur P, Sahu SK. Alpha-amylase as molecular target for treatment of diabetes mellitus: A comprehensive review. Chem Biol Drug Des. 2021;98(4):539-60.
12 Sadeghi M, Miroliaei M, Rahimmalek M, Taslimi P, Szumny A, Sadeghian N. Comparison of Flavonoid and Flavonoid Glycoside in the Inhibition of the Starch Hydrolyzing Enzymes and AGEs; A Virtual Approaches. J Oleo Sci. 2023;72(8):787-97.
13 Bhambhani S, Kondhare KR, Giri AP. Diversity in chemical structures and biological properties of plant alkaloids. Molecules. 2021;26(11):3374.
14 Heinrich M, Mah J, Amirkia V. Alkaloids used as medicines: Structural phytochemistry meets biodiversity—An update and forward look. Molecules. 2021;26(7):1836.
15 Bjørklund G, Shanaida M, Lysiuk R, Butnariu M, Peana M, Sarac I, et al. Natural compounds and products from an anti-aging perspective. Molecules. 2022;27(20):7084.
16 Zhao J, Wang Z, Karrar E, Xu D, Sun X. Inhibition mechanism of berberine on α-amylase and α-glucosidase in vitro. Starch-Stärke. 2022;74(3-4):2100231.
17 Nguyen DV, Hengphasatporn K, Danova A, Suroengrit A, Boonyasuppayakorn S, Fujiki R, et al. Structure—yeast α-glucosidase inhibitory activity relationship of 9-O-berberrubine carboxylates. Sci Rep. 2023;13(1):18865.
18 Stefanello N, Schmatz R, Pereira LB, Rubin MA, da Rocha JBT, Facco G, et al. Effects of chlorogenic acid, caffeine, and coffee on behavioral and biochemical parameters of diabetic rats. Mol Cell Biochem. 2014;388(1):277-86.
19 Marques L, Costa B, Pereira M, Silva A, Santos J, Saldanha L, et al. Advancing precision medicine: a review of innovative in silico approaches for drug development, clinical pharmacology and personalized healthcare. Pharmaceutics. 2024;16(3):332.
20 Vidal-Limon A, Aguilar-Toalá JE, Liceaga AM. Integration of molecular docking analysis and molecular dynamics simulations for studying food proteins and bioactive peptides. J Agric Food Chem. 2022;70(4):934-43.
21 Bai G, Pan Y, Zhang Y, Li Y, Wang J, Wang Y, et al. Research advances of molecular docking and molecular dynamic simulation in recognizing interaction between muscle proteins and exogenous additives. Food Chemistry. 2023;429:136836.
22 Şöhretoğlu D, Renda G, Arroo R, Xiao J, Sari S. Advances in the natural α-glucosidase inhibitors. Efood. 2023;4(5):e112.
23 Swain SS, Hussain T. Combined Bioinformatics and Combinatorial Chemistry Tools to Locate Drug-Able Anti-TB Phytochemicals: A Cost-Effective Platform for Natural Product-Based Drug Discovery. Chem Biodivers. 2022;19(11):e202200267.
24 Shakoor B, Yaqoob N, Shafiq N, Bin Jardan YA, Nafidi HA, Bourhia M. In silico ADME/Tox profiling of mushroom secondary metabolites. ChemistrySelect. 2024;9(4):e202304312.
25 Oner E, Al-Khafaji K, Mezher MH, Demirhan I, Suhail Wadi J, Belge Kurutas E, et al. Investigation of berberine and its derivatives in Sars Cov-2 main protease structure by molecular docking, PROTOX-II and ADMET methods: in machine learning and in silico study. J Biomol Struct Dyn. 2023;41(19):9366-81.
26 Firman JW, Boobis A, Hollnagel HM, Kaiser S, Lovell DP, Moretto A, et al. Evaluating the consistency of judgments derived through both in silico and expert application of the Cramer classification scheme. FCT. 2024;194:115070.
27 Xue Q, Liu X, Russell P, Li J, Pan W, Fu J, et al. Evaluation of the binding performance of flavonoids to estrogen receptor alpha by Autodock, Autodock Vina and Surflex-Dock. Ecotoxicol Environ Saf. 2022;233:113323.
28 Pettersen EF, Goddard TD, Huang CC, Meng EC, Couch GS, Croll TI, et al. UCSF ChimeraX: Structure visualization for researchers, educators, and developers. Protein Sci. 2021;30(1):70-82.
29 Yahaya M, Bakar AA, Stanslas J, Nordin N, Zainol M, Mehat M. Insights from molecular docking and molecular dynamics on the potential of vitexin as an antagonist candidate against lipopolysaccharide (LPS) for microglial activation in neuroinflammation. BMC biotechnology. 2021;21(1):38.
30 Sadeghi M, Seyedebrahimi S, Ghanadian M, Miroliaei M. Identification of cholinesterases inhibitors from flavonoids derivatives for possible treatment of Alzheimer's disease: In silico and in vitro approaches. CRSB. 2024;7:100146.
31 Mishra A, Kumar V, Kumar S, Singh H, Singh A.

HRAMS Proteomics Insights on the Anti-Filarial Effect of Ocimum sanctum: Implications in Phytochemical-Based Drug-Targeting and Designing. Proteomes. 2024;13(1):2.

32 Eker F, Duman H, Akdaşçi E, Bolat E, Sarıtaş S, Karav S, et al. A comprehensive review of nanoparticles: from classification to application and toxicity. Molecules. 2024;29(15):3482.

33 Ma B, Zhang H, Li R, Zhang S, Chen L, Zhou T, et al. Molecular-docking electrolytes enable high-voltage lithium battery chemistries. Nat Chem. 2024;16(9):1427-35.

34 Alagöz T, Çalişkan FG, Bilgiçli HG, Zengin M, Sadeghi M, Taslimi P, et al. Synthesis, characterization, biochemical, and molecular modeling studies of carvacrol-based new thiosemicarbazide and 1, 3, 4-thiadiazole derivatives. Arch Pharm. 2023:e2300370.

35 Israr J, Alam S, Siddiqui S, Misra S, Singh I, Kumar A. Advances in Structural Bioinformatics. Adv Bioinform: Springer; 2024. p. 35-70.