International Journal of Pharmaceutical and Clinical Research

ISSN Print: 2664-7591
ISSN Online: 2664-7605
Impact Factor: RJIF 8-16
IJPCR 2026; 8(1): 05-10
www.pharmaceuticaljournal.in
Received: 06-10-2025
Accepted: 09-11-2025

Dr. Ali Said Yussuf
Department of Surgery, The State University of Zanzibar, Tanzania

Dr. Siva Nageswara Rao Mekala
Department of Clinical Pharmacology, The State University of Zanzibar - Tanzania

Dr. Saravanan R
Department of Pharmacology, RVS Dental College and Hospital, The Tamil Nadu Dr. M.G.R. Medical University, Coimbatore, Tamil Nadu, India.

Dr. Chukwuma J Okafor
Department of Pathology, The State University of Zanzibar, Tanzania

Dr. Murugesan Annamalai
Department of Biochemistry, RVS Dental College and Hospital, The Tamil Nadu Dr. M.G.R. Medical University, Coimbatore, Tamil Nadu, India

Dr. Anand Paramasivam
Department of Physiology, RVS Dental College and Hospital, The Tamil Nadu Dr. M.G.R. Medical University, Coimbatore, Tamil Nadu, India

Corresponding Author:
Dr. Siva Nageswara Rao Mekala
Department of Clinical Pharmacology, The State University of Zanzibar - Tanzania

Computational characterization of antidiabetic phytochemicals from Gymnema Sylvestre: A molecular docking study of astragalin

Ali Said Yussuf, Siva Nageswara Rao Mekala, Saravanan R, Chukwuma J Okafor, Murugesan Annamalai and Anand Paramasivam

DOI: https://doi.org/10.33545/26647591.2026.v8.i1a.159

Abstract
Diabetes mellitus (DM), specifically type 2 diabetes, is a worldwide metabolic syndrome associated with such complications as cardiovascular disease, kidney failure and neuropathy. Although traditional medicines such as metformin and sulfonylureas are effective, their effect reduces with time, which creates a tendency to resort to alternative medicine. Gymnema sylvestre is a traditional medicinal herb that has bioactive compounds like Astragalin that have been proven to have antidiabetic effects. This paper has employed molecular docking which analyzes the interaction of Astragalin with the Human Multidrug Resistance Protein 1 Nucleotide Binding Domain 1 (PDB ID: 2CBZ) and compared the binding affinity of Astragalin to the interaction with Glibenclamide, a standard diabetes medication. The experiment results revealed that Astragalin had a similar MolDock score (-83.62) and more strong hydrogen bond interactions (-13.79) compared to Glibenclamide. These results indicate that Astragalin has a potential to become a rather successful alternative or complement to conventional antidiabetic drugs. The study needs further experimental confirmation to investigate its therapeutic application.

Keywords: Diabetes, Astragalin, Gymnema sylvestre, molecular docking, Glibenclamide

Introduction
Diabetes mellitus (DM), particularly type 2 diabetes, has emerged as one of the most prevalent chronic metabolic disorders globally, characterized by hyperglycemia resulting from either insulin resistance or insufficient insulin secretion. If left uncontrolled, diabetes can lead to serious complications, including cardiovascular disease, kidney failure, neuropathy and blindness [1-3]. While conventional pharmacological treatments, such as metformin and sulfonylureas, provide therapeutic benefits, they often come with side effects and their long-term efficacy can diminish due to drug resistance. Consequently, there is a growing interest in alternative and complementary approaches to manage diabetes, especially those based on natural products, which have long been used in traditional medicine for their therapeutic properties [4-6].

Gymnema sylvestre, a medicinal herb native to India and Africa, has been recognized for its potential in treating diabetes. It has been used in Ayurvedic medicine for centuries to regulate blood sugar levels and modern research has started to substantiate its antidiabetic effects [7, 8]. The active components of Gymnema sylvestre, particularly gymnemic acids, have been shown to possess a variety of pharmacological properties, including the ability to inhibit intestinal glucose absorption, enhance insulin secretion and improve insulin sensitivity [7, 9-11]. Gymnema has also demonstrated an ability to reduce blood sugar levels and the glycosylation of proteins, a process involved in the development of diabetic complications. Moreover, its antidiabetic effects extend beyond glucose regulation, as it also exerts anti-inflammatory and antioxidant effects, which are crucial for managing diabetes-related complications [12-14].

Recent advancements in computational chemistry have made it possible to better understand the molecular mechanisms behind the antidiabetic activity of natural products. Computational techniques, such as molecular docking, are now routinely employed to predict the binding affinities of bioactive compounds from plants to specific targets, such as

enzymes involved in glucose metabolism and insulin signaling [15-17]. By simulating the interaction between bioactive molecules and target proteins, researchers can gain insights into their potential mechanisms of action, identify new drug candidates and expedite the drug discovery process [18-21].

In this study, we aim to computationally characterize the antidiabetic phytochemicals present in Gymnema sylvestre. Using molecular docking-based screening, we will investigate the interaction of gymnemic acids and other bioactive compounds with key diabetes-related targets, such as alpha-glucosidase, dipeptidyl peptidase-4 (DPP-4) and peroxisome proliferator-activated receptors (PPARs). This study seeks to provide a deeper understanding of the mechanisms by which Gymnema sylvestre exerts its therapeutic effects, offering insights into the development of novel, plant-based antidiabetic therapies

Materials and Methods

Protein Preparation

The docking experiment was initiated by setting up of the target protein structures in Molegro Virtual Docker (MVD). The search of Protein Data Bank (PDB) was performed by the 3D crystal structure of Human Multidrug Resistance Protein 1 Nucleotide Binding Domain 1 (PDB ID: 2CBZ) because it has high-resolution data (less than 2.5 A), providing the accuracy and integrity of the structure. The protein structure was imported into the MVD workspace with the functionality of "File Import Molecule Protein" and optimized and refined [2, 5, 19, 22].

Unless needed to stabilize the ligand, the removal of water molecules was done and the removal of heteroatoms that were not necessary was also done to prevent interference during docking. Repair Add Missing Hydrogens tool was used to add polar hydrogens to ascertain good charge distribution and geometry. MVD was used to automatically give the correct atom types and bond orders to the molecular structure to give it consistency. The "Detect Cavities" functionality was applied to determine any possible binding sites on the protein. The active binding pocket which had been selected according to the best volume and lowest energy was selected to do additional simulations [23-26].

Ligand Preparation

In the molecular docking simulations, the ligand was selected as Astragalin which is a bioactive compound of Gymnema sylvestre. Besides, a conventional antidiabetic medication Glibenclamide was used as a control. The chemical structure of Astragalin was accessed in PubChem database either 2D or 3D format and saved in standard file formats [27-31].

Chem3D software was used to minimize the energy of the ligands, where MM2 or MMFF94 force field was used to achieve a stable geometry and a favorable structure of the ligand. This process minimized steric strain, optimized the bond angles and made the ligands take the most favorable energy conformation. The minimized structures in 3D format were then exported as either. mol2 or. sdf in order to be compatible with MVD. Ligands were imported in MVD in the file Import Molecule Ligand option and hydrogen atoms omitted to satisfy valence were added. MVD automatically fixed and transformed type atoms and bond orders to make the ligands ready to the docking simulations [27, 28, 32-34].

Molecular Import and Preparation

The target protein (Human Multidrug Resistance Protein 1 Nucleotide Binding Domain 1, PDB ID: 2CBZ) and the ligands (Astragalin and Glibenclamide) were imported into the MVD workspace in order to simulate docking. The protein and the ligands were maintained in their protonated state at a physiological pH (~7.4) to maintain the correct electrostatic potential and hydrogen-bonding patterns which are essential to rely on in docking results [24, 35].

Docking Wizard tool in MVD was used to identify the binding site. The active binding pocket was selected manually and the center coordinates (X, Y, Z) and radius (812 A) of the binding pocket were entered so that the docking algorithm could focus on the biologically active areas of the protein [36-38].

Docking Setup

In MVD, a docking project was generated via the menu of Docking start Docking wizard (Create new docking Job). MolDock SE (Simplex Evolution) algorithm was selected because it is an effective method of exploring the ligand conformational space. Scoring functions were employed to obtain the binding affinity based on the non-bonded interactions and steric complementarity, MolDock Score or Re-Rank Score [39, 40].

The following parameters were used in the docking simulation: Count of runs = 10-30, maximum iteration = 1500-2000 and population size = 50-100. The option of Docking Constrain was turned on to allow the specific interactions of the residues of the Human Multidrug Resistance Protein 1 Nucleotide Binding Domain 1 with the ligands. A threshold was established at 100 and a saving amount of 10-20 was reserved to be analyzed. After the parameters had been set up, the docking simulation was launched and the software executes repeated conformational searches until the best binding poses with lowest energy scores were located [41-44].

Docking Analysis

Following docking simulations, MVD produced a list of priority list of ligand-protein binding poses sorted by MolDock Scores (predicted binding energies). The most stable complex and one favorable to energy (the lowest score) constituted the pose of the most stable and favorable complex and correlated with the high affinity between the ligand and the protein active site [45, 46].

The View Ligand Interactions requirement in MVD was adopted to visualize the molecular interactions. This gave us fine details of hydrogen bond, hydrophobic and electrostatic interactions between Astragalin or Glibenclamide and the residues of Human Multidrug resistance protein 1 Nucleotide binding domain 1. The lengths of the bonds (in A) were measured and the amino acids interacting were measured to determine the stability and specificity of the interactions. The poses of the binding were compared to the ligands that were co-crystallized to confirm the validity of the docking [47-49].

Also the components of energy, hydrogen bonding, van der Waals forces, steric interactions, electrostatics and torsional penalties have been analyzed to give more details of the binding mechanism. The resulting final was exported either in.mol2, in pdb or in image format so as to carry out further analysis and visualization such as the generation of 2D, 3D and secondary interaction maps, used as publication figures.

Results

Docking analysis of Astragalini, a bioactive compound of Gymnema sylvestre and Glibenclamide, a common antidiabetic agent against Human Multidrug Resistance Protein 1 Nucleotide Binding Domain 1 (PDB ID: 2CBZ) showed promising results. Table 1 showed that Astragalin had a MolDock score of -83.62 compared to the score of Glibenclamide of -79.64 which is a bit higher and this implies that Astragalin has a similar binding affinity with the target protein or slightly better. This is also supported by the Rerank score where Astragalin had a score of -76.12 as compared to -33.05 of Glibenclamide indicating that Astragalin has a stronger and specific interaction with the protein. The hydrogen bond analysis also inclined towards Astragalin whose bond value was -13.79 which was highly strong than that of Glibenclamide (-2.46). This implies that Astragalin can interact more frequently and energetically favorably with the protein, which could also be one of the reasons that it has antidiabetic effects.

The binding modes of the two compounds with the protein are visually explained in the 2D, 3D and secondary interaction figures (Figures 16). Astragalin established a lot of hydrogen bond and hydrophobic interactions with the target protein thus having the potential to be a good antidiabetic agent. These results indicate that Astragalin might be a promising analogy to be experimentally validated and may be used as an alternative or supplement to other conventional diabetes agents such as Glibenclamide.

Discussion

Diabetes mellitus, especially type 2, is a huge health issue among the world and although treatment has been made available, the condition is proving hard to control. Traditional medications such as metformin and sulfonylureas are useful in the short-run but fail in the long-run because of adverse side effects and resistance to the drugs. Consequently, novel strategies are largely required and especially those grounded on natural products, which have been in use in traditional medicine since ancient times. Gymnema sylvestre is one of these plants that have been given attention due to its ability to cure diabetes. Its bioactive constituents, especially Astragalin, have been found to provide effective effects by various ways, which include enhancement of insulin sensitivity, inflammatory effects and glucose metabolism [7, 8, 22, 50-53].

Molecular docking and other computational techniques were applied in the present study to assess the potential of Astragalin as an antidiabetic agent. This study will shed light on the binding affinity and interactions between Astragalin and one of its targets because it was simulated with the Human Multidrug Resistance Protein 1 Nucleotide Binding Domain 1 (PDB ID: 2CBZ). The obtained results, summarized in Table 1, mean that Astragalin has a MolDock score of -83.62 which is slightly superior to the score of Glibenclamide, -79.64. Moreover, the Rerank score of Astragalin, -76.12, relative to that of Glibenclamide, -33.05 indicates that Astragalin can develop a more specific and stable interaction with the protein, which enhances its potential as a good therapeutic agent.

The analysis of hydrogen bond also confirms the superiority of Astragalin as the value of the bond is -13.79 and much higher than that of Glibenclamide which is -2.46. This suggests that Astragalin might have a more favorable and less energetically unstable contact with the protein, with a greater capacity to increase its effectiveness in the area of glucose metabolism regulation.

The visual illustrations of Figures 1-6 show how Astragalin forms strong hydrogen and hydrophobic bonds and interactions with the target protein and support its use as an antidiabetic agent. These findings are consistent with the past researches that have shown the therapeutic benefits of Gymnema sylvestre and its extracts in the management of diabetes. Indicatively, Gymnema sylvestre compounds have been reported to stimulate insulin release and lower the level of blood glucose in animal subjects, which attests to the antidiabetic properties of the compound.

Altogether, this paper indicates that Astragalin may be a prospective candidate of further clinical research and may become an alternative or supplement of traditional methods of treating diabetes, such as Glibenclamide. The validation of these in silico results as well as the establishment of the clinical applicability of Astragalin require future research, both in vitro and in vivo.

Table 1: Ranking of Ligands and Poses against human Multidrug Resistance Protein 1 Nucleotide Binding Domain 1 Protein Based on Moldock Score. Protein: 2CBZ

Ligand	Species Name	MolDock	Rerank	H Bond
5282102	Astragalin	-83.62	-76.12	-13.79
3488	Glibenclamide (Standard Drug)	-79.64	-33.05	-2.46

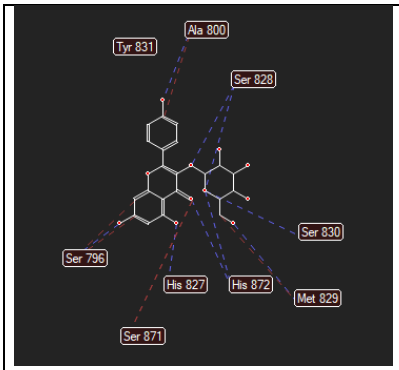

Fig 1: 2D Interaction

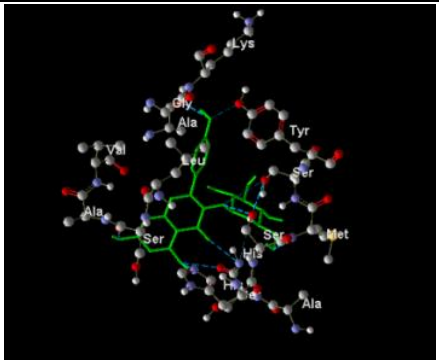

Fig 2: 3D Interaction

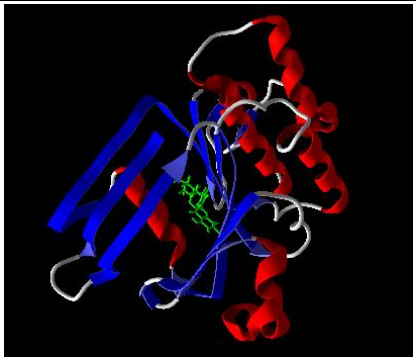

Fig 3: Secondary Interaction

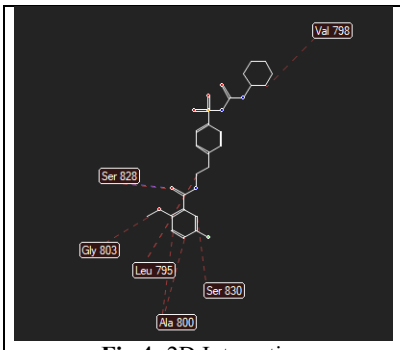

Fig 4: 2D Interaction

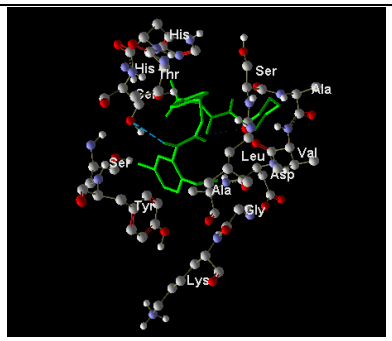

Fig 5: 3D Interaction

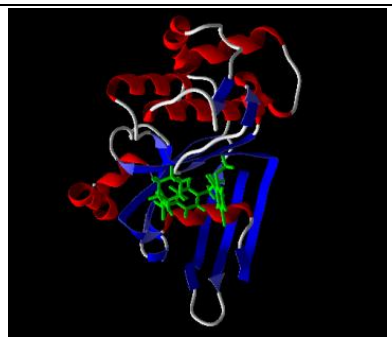

Fig 6: Secondary Interaction

Conclusion

This computational study presents the possibility of Astragalin, a bioactive compound of Gymnema sylvestre, to work as an antidiabetic drug. The molecular docking simulation revealed that Astragalin has a similar, or even greater, binding affinity to the Human Multidrug Resistance Protein 1 Nucleotide Binding Domain 1 (PDB ID: 2CBZ) to the antidiabetic drug Glibenclamide. The fact that the hydrogen bond interactions are stronger with Astragalin is an indication that maybe it provides a more stable and specific interaction with the target protein and supports its use as an alternative and/or supplement to the standard diabetes therapies. These results should be further tested in experimentation to verify them and discuss clinical use of Astragalin in managing diabetes.

Acknowledgments

We acknowledge the management, institutional heads, co-workers for their contribution and support and we declare that there is no conflict of interest related to the work.

References

1. Bidulka P, Smeeth L, Nitsch D, Silverwood RJ, Basu A, Adler AI, *et al*. Comparative effectiveness of second-line oral antidiabetic treatments among people with type 2 diabetes mellitus: emulation of a target trial using routinely collected health data. BMJ. 2024;385:e077097.
2. Choudhary AN, Tahir F. Therapeutic effect of *Gymnema sylvestre* extract against hyperglycemia: in vivo study. Agrobiological Records. 2023;14:50–58.
3. Libianto R, Davis TM, Ekinci EI. Advances in type 2 diabetes therapy: a focus on cardiovascular and renal outcomes. Medical Journal of Australia. 2020;212:133–139.
4. Ebadi AG. Synergistic approaches in diabetes management: the role of antidiabetic drugs and herbal medicine in therapeutic strategies. Nepal Journal of Medical Sciences. 2025;10:68–82.
5. Kakde N. Thermal analytical characterization of *Gymnema sylvestre* using TGA–DTA technique. Cana. 2025;32:883–888.
6. Muthu T, Adusumalli R, Vemuri SK, Indira Devi M, Pavan Kumar P, Banala RR, *et al*. Eco-biofabrication of silver nanoparticles from *Azadirachta indica*, *Gymnema sylvestre*, and *Moringa oleifera* for lung cancer treatment. Journal of the Egyptian National Cancer Institute. 2025;37.
7. Udrea AM, Gradisteanu Pircalabioru G, Boboc AA, Mares C, Dinache A, Mernea M, *et al*. Advanced bioinformatics tools in the pharmacokinetic profiles of natural and synthetic compounds with antidiabetic activity. Biomolecules. 2021;11:1692.
8. Khan F, Sarker MMR, Ming LC, Mohamed IN, Zhao C, Sheikh BY, *et al*. Comprehensive review on phytochemicals, pharmacological and clinical potentials of *Gymnema sylvestre*. Frontiers in Pharmacology. 2019;10.
9. Dewangan HK, Singh N, Kumar Megh S, Singh S, Lakshmi L. Optimisation and evaluation of *Gymnema sylvestre* extract-loaded polymeric nanoparticles for enhancement of in vivo efficacy and reduction of toxicity. Journal of Microencapsulation. 2022;39:125–135.
10. Gaytán Martínez LA, Sánchez-Ruiz LA, Zuñiga LY, González-Ortiz M, Martínez-Abundis E. Effect of *Gymnema sylvestre* administration on glycemic control, insulin secretion, and insulin sensitivity in patients with impaired glucose tolerance. Journal of Medicinal Food. 2020;24:28–32.
11. Li Y, Wang T, Zhang Z, Liu Y, Sun M, Liang J. Gymnemic acid ameliorates hyperglycemia through PI3K/AKT- and AMPK-mediated signaling pathways in type 2 diabetes mellitus rats. Journal of Agricultural and Food Chemistry. 2019;67:13051–13060.
12. Borah L, Sen S, Mishra M, Barbhuiya PA, Pathak MP. Therapeutic potential of genistein: insights into multifaceted mechanisms and perspectives for human wellness. Current Topics in Medicinal Chemistry. 2025;25:3190–3202.
13. Shi Y, Ma P. Pharmacological effects of Astragalus polysaccharides in treating neurodegenerative diseases. Frontiers in Pharmacology. 2024;15.
14. Soomro MA, Khan S, Majid A, Bhatti S, Perveen S, Phull AR. Pectin as a biofunctional food: comprehensive overview of its therapeutic effects and antidiabetic-associated mechanisms. Discover Applied Sciences. 2024;6.
15. Shah AB, Baiseitova A, Amzeyeva U, Shang X, Jenis J. α-Glucosidase inhibition-guided network pharmacology and molecular docking reveal the antidiabetic potential of *Cichorium intybus* as a functional food. International Journal of Molecular Sciences. 2025;26:9497.
16. Tipugade O, Sawale J, Jadhav N. Network pharmacology and molecular docking-based exploration of Rubiaceous plants for breast cancer: phytochemicals, preclinical studies, and regulatory perspectives. Asian Journal of Pharmaceutical and Clinical Research. 2025;18:52–71.
17. Ye JX, Wu JY, Zhu M, Ai L, Huang Q. Elucidating the role of *Gardeniae fructus* and *Scutellariae radix* herb

pair in Alzheimer's disease via network pharmacology. Cellular Physiology and Biochemistry. 2025;26.
18. Vijh D, Gupta P. GC–MS analysis, molecular docking, and pharmacokinetic studies on *Dalbergia sissoo* bark extracts for compounds with antidiabetic potential. Scientific Reports. 2024;14.
19. Ditchou YON, Leutcha PB, Miaffo D, Mamoudou H, Ali MS, Ngnoung GAA, *et al*. In vitro and in silico assessment of antidiabetic and antioxidant potencies of secondary metabolites from *Gymnema sylvestre*. Biomedicine and Pharmacotherapy. 2024;177:117043.
20. Oyinloye BE, Ajiboye BO, Dao TNP, Idowu OT, Mathenjwa-Goqo MS, Aruleba RT, *et al*. In silico comparison of bioactive compounds characterized from *Azadirachta indica* with an FDA-approved drug against schistosomal agents. Molecules. 2024;29:1909.
21. Muddapur UM, More SS, Manjunath S, Alqahtani YS, Khan AA, Shaikh IA, *et al*. Exploring bioactive phytochemicals in *Gymnema sylvestre*: biomedical uses and computational investigations. Separations. 2024;11:50.
22. Ononamadu CJ, Ibrahim A. Molecular docking and prediction of ADME/drug-likeness properties of potentially active antidiabetic compounds isolated from *Gymnema sylvestre* and *Combretum micranthum*. BioTechnologia. 2021;102:85–99.
23. Abd El-Nasser MG, Ismail TI. Synthesis, characterization, molecular docking studies, and theoretical calculations of novel Ni(II), Cu(II), and Zn(II) complexes based on benzothiazole derivative. BMC Chemistry. 2025;19.
24. Li Q, Yang Z, Lu H, Liu F, Zhou D, Zou Y. Astragalin exerted hypoglycemic effect by inhibiting α-glucosidase and modulating AMPK signaling pathway. Nutrients. 2025;17:406.
25. Zhao C, Zhang Q, Shui J, Liu J, Liu X, Wang J, *et al*. Molecular recognition regulates coordination structure of single-atom sites. Angewandte Chemie International Edition. 2023;62.
26. Da Y, Chen W, Xi S, Wang Y, Lian X, Jiang R, *et al*. Dual Pt–Ni atoms dispersed on N-doped carbon nanostructure for synergistic electrocatalytic hydrogen evolution reaction. Science China Materials. 2022;66:1389–1397.
27. Patra S, Paul A, Shand H, Ghosal S, Ghorai S. In silico identification of anticancer flavonoids as dengue virus replication inhibitors. Journal of Molecular Modeling. 2025;31.
28. Sharma G, Kumar N, Sharma CS, Alqahtani T, Tiruneh YK, Sultana S, *et al*. Identification of promising SARS-CoV-2 main protease inhibitors through molecular docking and dynamics simulation. Scientific Reports. 2025;15.
29. Dib H, Abu-Samha M, Younes K, Abdelfattah MAO. Physicochemical properties–activity relationship of novel PIM1 kinase inhibitors. Pharmaceuticals. 2024;17:880.
30. Elebiju OF, Ogunnupebi TA, Adebiyi E, Ajani OO, Oduselu GO. In silico design of potential small-molecule antibiotic adjuvants against *Salmonella typhimurium*. Pharmaceuticals. 2024;17:543.
31. Nikitha R, Afeeza K, Dilipan E, Suresh V. Molecular docking of seaweed-derived fucoxanthin against the monkeypox virus. Cureus. 2024;16.
32. Shahid H, Ibrahim M, Alonazi WB, Chi Z. Ellagitannin lead compounds for nonalcoholic fatty liver disease: computer-aided drug design approach. Computer-Aided Design. 2025;21:1108–1122.
33. Sierra-Hernandez O, Saurith-Coronell O, Rodríguez-Macías J, Márquez E, Mora JR, Paz JL, *et al*. In silico identification of potential clovibactin-like antibiotics. International Journal of Molecular Sciences. 2025;26:1724.
34. Pant J, Singh L, Mittal P, Kumar N. Valencene as a novel potential downregulator of THRB in NSCLC. Molecular Diversity. 2024;29:2543–2563.
35. Payen L, Trinquart Y, Guillouzo A, Courtois A, Delugin L, Fardel O. Glibenclamide inhibits multidrug resistance protein activity in human lung cancer cells. British Journal of Pharmacology. 2001;132:778–784.
36. Ma MY, Qian F, Mu GQ, Xu YP, Wu FY, Zhu XM. Interaction mechanism of whey protein isolate with phosphatidylcholine. Journal of Food Science. 2024;89:4109–4122.
37. Wang Z, Yang L, Xue S, Liu H, Wang S, Ma T, *et al*. Molecular docking and dynamic insights on adsorption effects of soy hull polysaccharides on bile acids. International Journal of Food Science and Technology. 2022;57:3702–3712.
38. Rai H, Dubey VK, Suresh A, Barik A, Singh YP, Modi G, *et al*. Molecular docking and dynamics of antiviral agents against SARS-CoV-2 main protease. Molecular Diversity. 2021;25:1905–1927.
39. Liu W, Liu R, Qin Q, Wang H, Zhang X, Meng G. Molecular docking and dynamics simulation of wheat gluten-derived antioxidant peptides. Journal of the Science of Food and Agriculture. 2024;104:8150–8161.
40. Sun J, Sai H, Nie Z, Duan J, Cheng J, Liu Y, *et al*. Interaction between fulvic acid and trypsin using spectroscopic and molecular docking techniques. Chemistry and Biodiversity. 2024;21.
41. Mukhopadhyay S, Roy C, Ghosh P. Spice components as modulators of P-glycoprotein: an in silico study. Indian Journal of Pharmacology. 2024;56:214–219.
42. Conrad J, Paras NA, Vaz RJ. Model of P-glycoprotein ligand binding and validation with efflux substrate pairs. Journal of Medicinal Chemistry. 2024;67:5854–5865.
43. Cheema Y, Linton KJ, Jabeen I. Molecular modeling studies of novel lead compounds against ABCB1. Biomolecules. 2024;14:114.
44. Lahyaoui M, Diane A, El-Idrissi H, Saffaj T, Rodi YK, Ihssane B. QSAR modeling and molecular docking of P-glycoprotein inhibitors. Heliyon. 2023;9:e13020.
45. Vidal-Limon A, Liceaga AM, Aguilar-Toalá JE. Integration of molecular docking and molecular dynamics simulations for food proteins. Journal of Agricultural and Food Chemistry. 2022;70:934–943.
46. Fukunishi Y, Nakamura H. Prediction of ligand-binding sites of proteins by molecular docking. Protein Science. 2010;20:95–106.
47. Pan L, Aller SG. Allosteric role of substrate occupancy toward alignment of P-glycoprotein nucleotide-binding domains. Scientific Reports. 2018;8.
48. Woodward OM, Guggino WB, Greenwell P, Cui J, Maloney PC, Parker BS, *et al*. Gout-causing Q141K mutation in ABCG2 leads to nucleotide-binding domain

instability. Proceedings of the National Academy of Sciences USA. 2013;110:5223–5228.
49. Loo TW, Bartlett MC, Detty MR, Clarke DM. ATPase activity of the P-glycoprotein drug pump. Journal of Biological Chemistry. 2012;287:26806–26816.
50. Cesar T, Oliveira MR, Sandrim V, Mendes A, Bruder R, Oliveira R, *et al*. Citrus flavonoid supplement enhances glycemic control in prediabetic patients. Frontiers in Nutrition. 2025;12.
51. Chauhan A, Patel SS. Thyroid hormone and diabetes mellitus interplay. Hormone and Metabolic Research. 2024;56(12):845–858.
52. Al-Kuraishy HM, Al-Gareeb AI, Batiha GE-S, Saad HM. Effect of metformin on fibroblast growth factor 21 in type 2 diabetes mellitus. Inflammopharmacology. 2023;31(4):1751–1760.
53. Foretz M, Guigas B, Viollet B. Glucoregulatory mechanisms of metformin in type 2 diabetes mellitus. Nature Reviews Endocrinology. 2019;15(10):569–589.