

In Silico Molecular Docking Study of Some Antidiabetic Herbs: Review

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ABSTRACT

A chronic metabolic disease that is becoming more prevalent worldwide, diabetes mellitus causes serious health issues as well as financial hardships. Although synthetic antidiabetic medications are readily available, interest in natural items as possible substitutes has grown due to their adverse effects, poor effectiveness, and long-term consequences. Because they are effective, have fewer side effects in clinical trials, and are reasonably priced, herbal medications are recommended to treat diabetes mellitus. For diabetes mellitus to be well managed, screening for antidiabetic medications is crucial. A thorough grasp of the medicinal potential of antidiabetic herbs is provided by the combination of network pharmacology and computational methods in in-silico research. Researchers can efficiently identify molecular targets, explore herb-compound-target networks, and look into the polypharmacology and synergistic effects of the herbs by fusing the concepts of network pharmacology with computational techniques like molecular docking, molecular dynamics, and omics technologies, as well as developments in generative artificial intelligence and machine learning. The present review article highlights the antidiabetic potential of some herbs including *Momordica Charantia*, *Azadirachta Indica*, *Gymnema sylvestre*, *Moringa Olifera*, *Ficus Lutea* Vahl, *Albisia Antunesiana*, and *Physalis angulata*. Screened through different In Silico molecular docking tools like Auto Dock, Vina, ADMET Predictor, Swiss Target Prediction, MOE Software, PyRx software, Flex AID, MedChem Studio. Phytochemicals from above drugs shows high binding affinities as comparing to standard reference drugs. The in-silico approaches comprehensively contribute to a deeper understanding of the molecular ligand target interaction of antidiabetic herbs and offer promising avenues for future drug development.

Keywords: Diabetes mellitus, In Silico, Molecular docking, Auto dock.

INTRODUCTION

Patients with diabetes, a chronic metabolic disease, either have insufficient insulin production or insulin resistance, a condition in which the body is unable to use insulin. This results in type 2 diabetes mellitus (T2DM), a disorder marked by elevated blood sugar levels. Oral hypoglycemic medications can be used to treat type 2 diabetes. Conversely, Type 1 diabetes mellitus (T1DM), commonly referred to as juvenile diabetes, is an autoimmune disease in which the patient's own antibodies damage the pancreatic β -cells, resulting in insulin insufficiency that can only be treated with insulin. According to a 2021 study, over 529 million people worldwide suffer with diabetes, and by 2050, that figure is expected to rise to 1.3 billion. T2DM affects the vast majority of people. Antidiabetic medications are widely used to

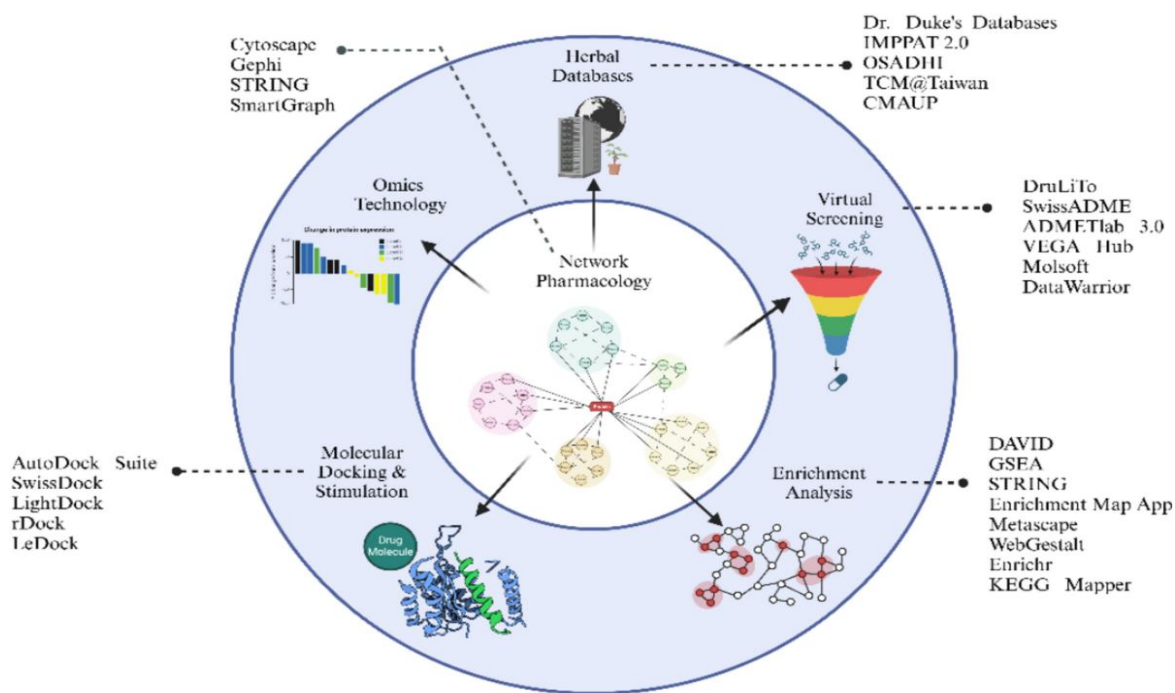
efficiently control blood sugar levels and lessen patient pain. Some of these medications include glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter-2 (SGLT2) inhibitors, biguanides, thiazolidinediones (TZDs), meglitinides, sulfonylureas, insulin sensitizers, insulin secretagogues, α -glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, and incretin mimetics.

These medications do have certain drawbacks, though, include drug responsiveness in individuals who don't reach glycaemic control and a number of other negative effects. Inconsistent meal patterns, poor eating habits, and the existence of comorbidities including obesity, hypertension, and renal or hepatic dysfunction are some of the reasons why glycaemic control is not achieved. Long-term poor glycaemic

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management is linked to the emergence of microvascular and macrovascular problems. The investigation of plant-derived chemicals, which are linked to fewer side effects and equivalent or higher therapeutic efficacy, has been made easier by recent

developments in the pharmaceutical sciences. Through a variety of processes, herbal extracts—complex blends of various phytochemicals—not only help achieve glycaemic control but also lessen the problems associated with diabetes.



Network pharmacology showing various computational technique

Since the beginning of human history, herbal plants have been utilised as medicine, and for ages, they have been the mainstay of diabetic treatment. The 5000-year-old Sumerian clay tablet has the earliest known written record of herbs being used as medicine. According to the World Health Organization (WHO), about 40% of pharmaceutical medicines are currently recognised to be derived from plants and traditional knowledge. Generally speaking, plants are abundant in secondary metabolites that serve as therapeutic agents to treat human illnesses. Alkaloids, bibenzyls, phenanthrenes, stilbenoids, phenols, flavonoids, anthocyanins, and polysaccharides are examples of secondary metabolites. Research has demonstrated that these compounds have lipid-lowering, anti-inflammatory, antibacterial, anthelmintic, anticoagulant, and antioxidant qualities.

MOLECULAR DOCKING

The process of predicting how small molecules will interact with larger macromolecules, including proteins, enzymes, DNA, or RNA, is known as molecular docking. With the use of this technique, scientists can better comprehend the location, strength, and potential consequences of molecular binding interactions[3]. The two primary phases of molecular docking are scoring and searching. Similar to determining the ideal fit for a key in a lock, the approach searches for potential ways the molecules could fit together. These potential fits are then assessed in the scoring process, which assigns a ranking based on how well they match.[4]

The term *in silico*, meaning “performed on computer or via computer simulation,” is derived from the concepts of *in vivo* and *in vitro*. The United States Environmental Protection Agency (EPA) defines the term *in silico* as the “integration of modern computing

and information technology with molecular biology to improve agency prioritization of data requirements and risk assessment of chemicals” [1,2].

A computer-aided in-silico simulation method called "in silico molecular docking" is used in drug design to forecast the orientation, binding affinity, and mode of interaction of ligands (such as medicinal compounds) with target proteins. It entails building compounds for possible medicinal applications, maximising molecular compatibility, and simulating interactions. This strategy has several benefits, such as environmental sustainability because it uses less solvents, disposes of electronic debris less frequently, and emits fewer greenhouse gases. By minimising the use of animals in research, it also conforms to the core ideas of the 3Rs (replacement, reduction, and refinement). Additionally, it lowers expenses, saves time, and enables the examination of physical and chemical properties.[4]

In silico investigations use a variety of methods, but the Target-Based Virtual Screening (TBVS) approach—also referred to as structure-based virtual screening—often uses docking and molecular dynamics. This method makes use of structural data about the target protein or receptor and makes it easier to find novel medications and complementary therapies to treat illnesses[4,10]. One popular structure-based in silico technique for predicting the binding modalities and affinities of small compounds and the target receptor is molecular docking. All potential binding modes' conformations are sampled, multiple poses representing the ligand's location within the protein's active site are created, and these conformations are ranked using scores to separate the right poses from the wrong ones. This makes it possible to estimate the protein-ligand interaction affinity, which aids in determining the most likely binding mechanism.[13].

Many of the plants on the list have the potential to be rediscoverable, and contemporary drug development efforts depend on the scientific validation of these plants using computational technologies. Here, computational techniques are essential because they allow for more effective bioactive chemical screening and analysis, which speeds up the search for possible antidiabetic drugs.

Herbs that should be studied using in silico molecular docking method

1) MOMORDICA CHARANTIA (Cucurbitaceae,) is generally called as bitter gourd. Its extract has a reputation for successfully reducing blood glucose levels. Insulin-like peptides, vicine, polypeptide-P, alkaloids, charantin, sterol glycosides, mcIRBP, triterpenoids, cucurbutanoid compounds, flavonoids, and phenols are among the several hypoglycemic substances that have been identified from *M. charantia*. A total of thirty-seven peptides from polypeptide-P of *M. charantia* were prepared including tetra-, penta-, and hexapeptides. This study involves the docking of thirty-seven peptides devised from polypeptide-P of *M. charantia* against IR as agonists and against SGLT1, DPP IV, and GLUT2 as inhibitors. The docking analysis was performed using Molecular Operating Environment (MOE) software. The three-dimensional (3D) structures of IR, SGLT, LUT2, and human dipeptidyl peptidase-IV as receptor proteins were retrieved from the RCSB Protein Data Bank in pdb format. The protein sequence of polypeptide-P from *M. charantia* was retrieved from NCBI's Entrez Protein. Molecular docking analysis was carried out to identify the best agonists of IR and inhibitors of SGLT1, DPP-IV, and GLUT2. The site finder tool of MOE was used to predict the active sites of both receptor proteins. MD simulations were conducted using the AMBER20 suite of molecular dynamics program with the force field FF14SB. The best selected peptides were further evaluated through admetSAR server to check their pharmacokinetics or ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiling.

All these studies were compared with Phlorizin (has been reported as an inhibitor of SGLT1) and therefore selected as a positive control in this study.

The dynamics stability of the receptors (i.e., IR and SGLT1) in the presence of the filtered peptides was investigated by running 50ns of molecular dynamics simulations. The structural stability of receptors was evaluated first by calculating root mean square deviation (RMSD) analysis, which computes structural deviations by overlapping simulation snapshots over docking reference snapshot based on carbon alpha atoms. Both complexes were revealed



stable as the RMSD was in good acceptable. The RMSD plot of both complexes was found very consistent, and no major deviations were reported.

The study suggested that, using an in silico approach, they discovered, designed, and proposed novel antidiabetic peptides for oral administration. Upon investigating dynamics stability, it was found that both complexes (i.e., LIVA-IR and DFGAS-SGLT1) were revealed to be stable as the RMSD values of both complexes were in good acceptable range. These ligands might reduce dependency on painful subcutaneous administration of insulin and on other drugs with a number of side effects. Out of thirty-seven peptides, the peptides LIVA, TSEP, EKAI, LKHA, EALF, VAEK, DFGAS, and EPGGGG were found to be the best ones as potential antidiabetic agents based on their interaction studies through molecular docking. These ligands were strictly evaluated through Lipinski's rule of five and ADMET profiling which strongly supported their antihyperglycemic properties, and therefore, these natural bioactive compounds would act as agonist of IR and inhibitors of SGLT1, DPP IV, and GLUT2 and may lead to design potential drugs to combat diabetes with fewer or no side effects.

2) AZADIRACHTA INDICA L., commonly known as neem, an evergreen tree in the Azadirachta genus and the Meliaceae family. Traditionally, neem has been used in South Africa, Nigeria, India, and other countries to treat a variety of ailments, including diabetes. It contains ascorbic acid, azadiradione, gallic acid linolenic acid, arabinose, nimbidol, nimbine, quercetin, and scopoletin. In this study, molecular docking is employed to assess the binding interactions between *A. indica* phytochemicals and human pancreatic α -amylase and α -glucosidase, which play key roles in DM. This study employed the PASS prediction tool to assess the potential bioactivity of various chemical compounds from *A. indica* and their co-crystals. Chemical structures were analyzed using the PASS platform. From the existing literature review, three-dimensional (3D) crystallographic structures of selected enzymes—human pancreatic α -amylase and α -glucosidase were gathered from the RCSB Protein Data Bank. The enzymes were prepared by eliminating unwanted superfluous elements such as enzyme chains, lipids,

heteroatoms, and water molecules with the help of Discovery Studio Visualizer. Several bioactive phytochemicals isolated from *A. indica* were selected that showed potential antidiabetic activity in different preclinical test. The ligands were prepared using Discovery Studio Visualizer. The PyRx software was used to perform molecular docking. Molecular docking was performed of metformin and phytochemicals of *A. indica* with the enzymes (4W93 and 3CTT) to determine binding affinity. pkCSM is a computational approach for pharmacokinetic property prediction in drug discovery.

Employing molecular docking, probable binding energies and ligand-receptor interactions were identified. They found that 24-MCL, SML, and BSL exhibit strong binding affinities with α -amylase, surpassing the commonly accepted threshold of -6.0 kcal/mol, suggesting stable enzyme inhibition. Researchers found that HBs have a significant impact on drug discovery and development. Drug-likeness estimation is critical for virtual evaluations of potential drugs. The Lipinski Rule of 5 assesses drug-like physicochemical qualities, with emphasis on criteria such as MW, lipophilicity, HB donors, and acceptors. MW, lipophilicity, hydrogen bonding, and other important characteristics are evaluated to determine possible drug candidates using Lipinski's Rule of 5, which ensures that the compounds have favorable pharmacokinetics. The analysis revealed from the study that the solubility parameter ranging from -1.185 to -6.773 log mol/L. Additionally, evaluating several parameters, including Caco-2 permeability, human intestinal absorption, VDss (human), BBB permeability, CYP450 1A2 inhibitor, CYP450 2D6 substrate, total clearance, renal OCT2 substrate, maximum tolerated dose, and AMES toxicity.

These study of phytochemicals done by comparison with drug Metformin as a standard drug.

This study carried out investigation of *A. indica* phytochemicals as potential inhibitors of human pancreatic α -amylase and α -glucosidase, two key enzymes involved in managing postprandial hyperglycemia. Through in silico molecular docking, the research identifies key compounds, such as 24-MCL, CTN, SML, BSL, and GN, demonstrating



exceptional binding affinities with these enzymes, suggesting their potential to effectively reduce blood glucose levels. These compounds have not previously been highlighted in literature as dual enzyme inhibitors, underscoring their novelty and therapeutic promise.

This study showed that *A. indica* has strong anti-diabetic effects, as do its bioactive phytochemicals, including 24-MCL, CTN, SML, BSL, and GN. The phytochemicals' positive ADMET profiles and pharmacokinetics further demonstrated their safety and effectiveness in the treatment of diabetes. Their antidiabetic potential was further validated by PASS prediction analysis, especially as α -amylase and α -glucosidase inhibitors.

3) MORINGA OLEIFERA (Moringaceae) leaves have been shown to include saponins, carotenoids, tannins, anthocyanins, alkaloids, glycosides, anthraquinones, steroids, flavonoids, and terpenoids. The chemical components of *M. oleifera*'s leaves play a vital role in several pharmacological processes that address diabetic problems and risk factors, anthocyanins, sitoglucoside, quercetin, anthraquinones, (glycosides), tannins, steroids, phenolics, and kaempferol showed antidiabetic and obesity activities

Using molecular docking, the chemicals in the extract of *M. oleifera* leaves were examined for their ability to bind in the mutant diabetes receptor kinase domain in association with cis-(R)-7-(3-(azetidin-1-ylmethyl) cyclobutyl)-5-(3-((tetrahydro-2H-pyran-2-yl) methoxy) phenyl)-7H-pyrrolo [2,3-d] pyrimidin-4-amine. Five substances were identified as meeting Lipinski's rules: anthraquinone, hemlock tannin, sitoglucoside (glycoside), phenolic steroid, 2-phenylchromenylium (anthocyanin), and others. These compounds also demonstrated some molecular interactions with the receptor through van der Waals interaction. By demonstrating significant affinities toward SGLT-2, GLP-1, and peroxisome proliferator-activated receptor gamma on quercetin and kaempferol, docking experiments were also conducted employing those receptor proteins. While kaempferol complied with VERBER's rule and Lipinski's rule of five out of the four requirements for drug-likeness prediction, quercetin showed the highest affinity for the SGLT-2 receptor. The targeted

enzyme, α -glycosidase, was used in another docking test. While interacting with residues ARG442 and GLU411 at the catalytic site, myricitrin, quercetin, and polydatin bound to the main site. The GLUT4 transporter, another protein target in antidiabetic research, was most receptive to kaempferol.[33] Stevioside showed an energy affinity of -6.893 kcal/mol, which was close to the cocrystallized ligand of α amylase with -7.811 kcal/mol. Compounds in *M. oleifera* leaf extract were assessed for their effects on α -amylase, α -glucosidase, and DPP-4. Additionally, it was shown that butyloxycarbonyl oxy-1 had an energy affinity of -5.583 kcal/mol, which was comparable to the cocrystallized ligand of DPP-4, α -amylase, and α -glucosidase (-6.102 kcal/mol).

This study shows that Flavonoids, such as quercetin and kaempferol, and nonflavonoids, such as anthraquinones, sitoglucoside (glycosides), hemlock tannins, phenolic steroids, and 2-phenylchromenylium (anthocyanin), found to exhibit insulin-resistant antidiabetic activity in in silico studies of *M. oleifera*.

4) GYMNEMA SYLVESTRE (Asclepiadaceae) and **Combretum micranthum** (Combretaceae) is a perennial, woody climber belonging to the family Asclepiadaceae and is an undomesticated shrub species. In addition to other phytochemicals like gurmardin (a polypeptide), flavonoids, anthraquinones, alkaloids, various acids (tartaric, formic), and plant sterols (stigmasterol), it contains triterpene saponins (such as gymnemic acids, gymnemasides, and gymnemasaponins) that give it its sweet-suppressing and anti-diabetic properties present in *G. sylvestre* leaf. *G. sylvestre* leaf extracts are used ethnopharmacologically to treat adult onset diabetes mellitus (NIDDM) and have been demonstrated to lower hyperglycemia in experimental animals. Another intriguing consequence of consuming *C. micranthum* tea is the regulation of blood glucose in diabetics. This study conducted molecular docking and screening of ADME/drug-likeness properties of the identified potentially active candidate compounds from aqueous-methanol extracts of *G. sylvestre* and *C. micranthum* leaves by using an in silico pharmacoinformatics approach with a view to validate and prioritize promising compound. Molecular docking of compounds from *G. sylvestre* and *C. micranthum* were performed on target proteins



(α -amylase, α -glucosidase, and phosphorylated insulin receptor tyrosine kinase). Compounds were isolated and were identified by LC-MS analysis. All the structural data of the identified compounds and acarbose were downloaded from PubChem or drawn with PubChem sketcher. The X-ray crystal structure data of human transferase (phosphorylated insulin receptor tyrosine kinase) and its analog; α -glucosidase, and human pancreatic α -amylase were downloaded from the RCSB database. All ligand structures were taken from Spartan 14 software. Docking simulations were performed using Molsoft ICM-pro 3.8-3. The ligands were scored using the Biased Probability Monte Carlo (BPMC) procedure. The in silico ADME screening and drug-likeness evaluation were performed using the free web tool SwissADME. The compounds with high-ranking binding energy scores were subjected to this part of the screening process. Simple physicochemical properties such as molecular weight (MW), molecular refractivity (MR), atom counts, and polar surface area (PSA) were computed. Drug-likeness candidature was implemented by Lipinski (2001), Ghose (1999), Veber (2002), Egan (2000), and Muegge (2001) rules of 5 (RO5) screening. Bioavailability scores, Lipophilicity, solubility were also checked. The computed ADMET properties (gastrointestinal (GI) absorption; blood-brain barrier (BBB) permeation inhibition of the cytochrome P450 system; permeability glycoprotein (P-gp) substrate) of these compounds were studied.

The observed docking scores (binding energy) were comparable to that of the reference drug L (acarbose).

This study investigated potential antidiabetic compounds identified from *G. sylvestre* and *C. micranthum* extracts by using in silico techniques. Furthermore, the drug-likeness screening of the promising compounds identified (prioritized) four drug like and lead-like candidates: E (4-hydroxycinnamic acid), F ((-)-11-hydroxy-9,10-dihydrojasmonic acid), H (gly inflanin A), and J (3-deshydroxysappanol trimethyl ether) shows the antidiabetic potential with some of the identified compounds showing strong binding affinity with target proteins relative to the reference drug (acarbose).

5) FICUS LUTEA VAHL (Moraceae), is commonly referred to as the African wild fig or yellow leaf rock fig. It contains diverse bioactive compounds, including specialized ceramide glycosides (e.g., luteoside), triterpenoids (-amyirin, lupeol, betulinic acid), sterols (-sitosterol), and phenolic compounds (tannins, flavonoids). This distinctive fig tree species is native to various regions of Africa.

Studies have highlighted the antidiabetic potential of *F. lutea* leaf crude acetone extract. This potential was demonstrated through the inhibition of digestive enzymes (α -amylase and α -glucosidase), stimulation of glucose utilization in muscle and adipocytes, and the insulin-releasing action of insulinoma cells. The in-silico antidiabetic activity was conducted via molecular docking technique using Auto Dock Vina between ligands and targeted enzymes involved in glucose metabolism to obtain free binding energy. The structure of compound were taken from pubchemncbi website and converted to required format the Auto Dock Tools. The 3-D of the various receptors: α -amylase, α -glucosidase, glycogen phosphorylase (GP); Peroxisome Proliferator-Activated Receptor Gamma (PPARG), Dipeptidyl peptidase 4 (DPP-IV), Glucokinase (GK), Protein Tyrosine Phosphatase 1B (PTP1B), and glucose transporter 1 catalytic site (GLUT1) were retrieved from the protein data bank. The cavity with the highest D-score value suggests more druggable sites that were selected as docking regions. The docking study was validated by re-docking the reference ligand into the appropriate protein cavity, and acceptable where the root mean square deviation (RMSD) value is <2.0 Å. The simplified molecular-input line-entry system (SMILES) formats of each isolated compound were retrieved from the PubChem server and used for in silico prediction. ADME profiles (absorption, distribution, metabolism, and excretion), were run on the Swiss ADME web server and the pkCSM web server. The drug-likeness of compounds based on Lipinski's rule of five was also predicted with the SwissADME web server, while the toxicity analysis was carried out by the ProTox-II web server.

The five isolated compounds' two-dimensional structures were compared to those of the positive



controls, which included metformin, gliclazide, rosiglitazone, sitagliptin, and acarbose.

This study found that the antidiabetic potential of compounds isolated from *F. lutea*'s ethyl acetate fraction with their inhibitory effects on α -glucosidase activity, glucose utilization enhancement, and apparent binding interactions with key receptors emphasize their therapeutic promise. This demonstrates that epiafzelechin and epicatechin in the ethyl acetate fraction of *F. lutea* are potential antidiabetic drugs and that they have the best drug-like qualities when compared to acarbose.

6) ALBIZIA ANTUNESIANA, a member of the Mimosaceae family, has been employed in traditional medicine in Zambia for its purported therapeutic properties. Numerous substances, such as triterpenoids, coumarins, and aromatic phenolic compounds, have been identified as having potential for treating diabetes. Mimosaceae medicinal plants are known for their many therapeutic applications.

Fifty eight (58) metabolites were tentatively identified using GNPS. even ligand molecules (Fig. 2) were selected from the phytochemicals identified in the root of *A. antunesiana*, as listed in Table S1. These phytochemicals were tentatively identified through mass spectrometry and molecular networking tools. The three-dimensional crystal structure of human SGLT2-MAP17 complex with Empagliflozin was retrieved from the Protein Data Bank. Docking simulations were performed using Auto Dock Tools. The selected ligand molecules and the reference drug were docked to human protein, SGLT2-MAP17, with the protein treated as a rigid body and the ligands allowed flexibility. The docked conformation with the lowest binding energy was selected to analyze the binding mode. Typically, the best docked conformation is determined by the lowest binding energy (> 5 kcal), which often correlates with biologically relevant interactions. ADMET analysis is essential for determining pharmacodynamics properties of a molecule done with using the web-based platform SWISSADME. Ligand SMILES structures retrieved from PubChem were submitted to SWISSADME for this evaluation. Toxicity of the metabolites was analyzed and predicted using the online web tool ProTox-II. In silico docking study

was performed to assess the inhibitory potential of specific metabolites on the target protein 7VSI. MD simulations and free energy calculations were performed. The ADMET and drug likeness properties for seven metabolites (L1 to L7) of *A. antunesiana* and reference antidiabetic drug, Empagliflozin, were evaluated to understand their potential as therapeutic agents.

Empagliflozin functions as SGLT2 (sodium-glucose co-transporter 2) inhibitor, effectively lowering blood glucose levels by promoting glucosuria. This established mechanism of action provides a clear target for identifying new antidiabetic compounds with similar or complementary effects. For this reason it is selected as a reference drug.

This study provides a comprehensive evaluation of seven metabolites from *Albizia antunesiana* as potential antidiabetic agents, comparing them to Empagliflozin through molecular docking, ADME, and toxicity analyses. Docking results identified L1 (8-Prenylnaringenin), L4 (8,8-dimethyl-2,10-dioxo-9H-pyrano [2,3-f]chromen-9-yl) (Z)-2-methylbut-2-enoate), and L7 (6-(4-sulfophenyl)octa noic acid) as having strong binding affinities, while ADME results showed favorable drug-likeness and high gastrointestinal absorption for most metabolites. Toxicity analysis highlighted L2 and L3 as the safest candidates, with low toxicity risks.

7) PHYSALIS ANGULATA L., which belongs to the Solanaceae family and is commonly referred to as cut leaf ground cherry. This plant has been traditionally used in various regions for its antibacterial, anti-inflammatory, and antidiabetic properties. Studies have shown that *Physalis angulata* L. contains alkaloids, withanolides, steroids and flavonoids that are known to exhibit potent biological activities.

The secondary metabolites *Physalis angulata* analyzed were sourced from the KNApSACk Family Database and Dr. Duke's Phytochemical and Ethnobotanical Database. Molecular structures were downloaded in Structure Data File (SDF) format and converted into 3D representations using Marvin Sketch software, which also facilitated structural optimization and visualization. The biological activities and protein targets of *Physalis angulata* L.



metabolites were predicted using Way2Drug PASS Online and Swiss Target Prediction. Protein-protein interactions were analyzed using the STRING database. The interaction between metabolites and proteins was further examined using the STITCH database. The (ADME) profiles of *Physalis angulata* L. metabolites were evaluated using Molsoft and SwissADME tools. Molecular docking simulations were conducted to evaluate the binding interactions between *Physalis angulata* L. metabolites and key antidiabetic target receptors. Metabolite structures were optimized using Marvin Sketch and converted to PDBQT format in AutoDock Tool. Docking simulations were performed using AutoDock. The interaction network between identified plant metabolites and their target proteins was constructed using STITCH, with visualization based on a confidence view. The pharmacokinetic properties and toxicity predictions of the identified plant metabolites were evaluated through ADMET. Molecular docking analysis revealed that quercetin and myricetin from *Physalis angulata* L. exhibit strong binding affinities to key antidiabetic targets.

This study demonstrates the potential of *Physalis angulata* L. metabolites, especially quercetin and myricetin, as multi-target antidiabetic agents. Molecular docking and MM/PBSA analyses revealed strong binding affinities with key diabetic targets, including aldose reductase, GLP-1 receptor, PPAR- γ , SGLT-2, AMPK, and GLUT4. Myricetin showed superior binding to aldose reductase (-89.211 kJ/mol) and GLP-1 (-92.952 kJ/mol), supporting its role in preventing complications and enhancing insulin secretion. Quercetin exhibited stronger interactions with SGLT-2 (-84.237 kJ/mol) and PPAR- γ (-80.340 kJ/mol), indicating its potential in glucose transport and lipid regulation. Myricetin and quercetin, Both compounds also interacted favorably with AMPK and GLUT4, reinforcing their effects on energy balance and glucose uptake

RECENT DEVELOPMENTS AND INNOVATIONS

Recent developments in AI and ML are revolutionising drug discovery by making it possible to find possible therapeutic candidates more quickly

and effectively, optimise lead compounds, and forecast medication attributes like efficacy and toxicity. In important domains like target discovery, virtual screening, property prediction, clinical trial design, de novo molecule design, and personalised medicine, these technologies aid in the quicker development of novel treatments with better patient outcomes.[17]

AI and ML are essential to diabetes research because they speed up the development of novel therapies and enhance disease control. AI can improve the accuracy of medication development by analysing large genomes and proteomics databases to find possible diabetes-related therapeutic targets [19]. Machine learning methods greatly cut down on research time and expense by enabling quick screening of chemical compounds to identify viable candidates for the treatment of diabetes[17]. By using cutting-edge machine learning algorithms to create novel compounds and forecast their properties, generative artificial intelligence (GenAI) has completely changed the drug discovery process. GenAI predicts crucial characteristics like solubility, stability, and binding affinity by using models like variational autoencoders (VAEs) and generative adversarial networks (GANs) to generate novel molecular structures based on training data[18]. Early phases of drug development are accelerated by these technologies' speed and efficiency, which lowers the expenses related to intensive experimental testing. When GenAI is combined with conventional computing techniques, prediction accuracy and dependability are increased. Nonetheless, there are still issues with the moral application of GenAI in drug discovery.

CONCLUSION

The present review highlights the antidiabetic potential of compounds isolated from *Momordica charantia*, *Moringa oleifera*, *Gymnema sylvestre*, *Ficus lutea* Vahl, *Albizia antunesiana*, *Physalis angulata*, and *Azadirachta indica*, studies by the in silico molecular docking technique. Various tools such as AutoDock, Vina, ADMET Predictor, Swiss Target Prediction, LeDock, Flex AID, MedChem Studio were used for the prediction and drug likeness. Emerging hybrid frameworks that combine traditional



medicine with modern computational tools hold promise for identifying novel bioactive compounds with multitarget capabilities. Furthermore, advancements in generative AI technologies and hybrid machine learning models are expected to redefine the scope of virtual screening, de novo drug design, and optimization, paving the way for more efficient and cost-effective therapeutic innovations in diabetes management.

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