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Advancing Type 2 Diabetes Mellitus Treatment with Computer Aided Drug Design

Research Article

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Abstract

Diabetes Mellitus is a worldwide chronic metabolic disorder characterized by pancreatic cell damage, or insulin resistance, and relative insulin insufficiency. Diabetes is also known as the third killer in humans after cancer and heart attack. This project seeks to tackle the prevalent global health challenge of diabetes mellitus through the application of in silico methods, a promising avenue in drug discovery and development. Our primary objective is to identify therapeutic targets for diabetes treatment, with a specific focus on Peroxisome Proliferators Activated Receptor Gamma (PPAR-γ) and Glycogen Phosphorylase (GP). Utilizing in silico techniques, we aim to explore the interaction of these targets with potential therapeutic agents to develop more potent treatments. Our project is centered on investigating the therapeutic potential of Organo Sulfur Compounds and understanding their interaction mechanisms with receptors using in silico techniques. The overarching aim is to expedite the discovery of novel, efficient, and safe treatments for diabetes mellitus. Computational tools like PyRx, SwissADME, Biovia Discovery Studio, ADMET SAR were used to check the binding and drug forming abilities of ligands under study. It is a faster and more accurate process as compared to the actual experimental trial and error method. Databases like PubChem, PDB and NCBI were also used. In addition to these the other software that were used are SwissADME, Marwin Sketch and OSIRIS data explorer.

Keywords: Diabetes, Organo sulfur compounds, Computer Aided Drug Design, PPAR-γ, GP, Insulin resistance.

Introduction

DM or Diabetes Mellitus is a worldwide inveterate metabolic condition characterized by pancreatic cell damage, or insulin resistance, and relative insulin insufficiency(1). Threat factors include inheritable, environmental, and behavioral factors. It can invoke several kinds of health problems, including neuropathy, cardiovascular problems, and kidney problems(2). In 2017, roughly 462 million people were affected by type 2 diabetes corresponding to 6.28% of the world's population (4.4% of those aged 15–49 years, 15% of those aged 50–69, and 22% of those aged 70+), or a commonness rate of 6059 cases per 100,000 (3). 529 million individuals globally had diabetes in 2021(4).Type 1 diabetes is characterized by an autoimmune response to pancreatic cells, whereas type 2 diabetes is caused by pancreatic beta cell failure(5).

Type 1 diabetes is generally diagnosed in children less than 15 years and adolescent grownups, but it can develop at any age(6)

Type 2 diabetes: With this type, your body does not make enough insulin and/or your body's cells do not respond generally to the insulin (insulin resistance). This is one of the most common type of diabetes(7). Type 2 diabetes is more likely to develop due to the consequences of gestational diabetes, which includes obesity, cardiovascular disease, and impaired carbohydrate metabolism(8).

Gestational diabetes: This type develops in some people during pregnancy. Gestational diabetes generally goes off after gestation. In spite of that, if you have gestational diabetes, you are at a advanced threat of developing Type 2 diabetes afterwards in life(9)

Prediabetes: Prediabetes is called the stage before Type 2 diabetes. Blood glucose positions are advanced than normal but not high enough to be officially diagnosed with Type 2 diabetes(10).

Ketoacidosis and hypoglycemia are two acute consequences of diabetes that are substantially brought on by hormonal imbalances caused by inadequate insulin(11). Insulin resistance and faults in insulin secretion are the primary causes of this disorder, which may be linked to obesity and neuroendocrine function which is a major factor in the development of type 2 diabetes(11). Diabetes, heart complaints, and asthma are some of the inveterate illnesses that obesity significantly increases the threat of, leading to a global pandemic (12). In present pharmacological support, phytomedicines, secondary metabolites deduced from plants are safe alternatives for synthetic drugs that have pharmacological or toxicological effects on people and creatures(13). Several plants have been suggested as possible treatments for controlling diabetes mellitus (14). Organosulfur compounds (OSCs), naturally

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present in plants contain Sulphur and have displeasing odor aiding in the prevention and treatment of life-threatening diseases. Organo Sulphur Compound such as Methiin Alliin, N-acetyl cysteine, S-ethyl cysteine were found to be present in Onion(15,16). Ajoene, Allyl propyl disulfide, Sallylcysteine, Allixin were found in Garlic(17). There are multiple target receptors which play a major part in diabetes as they regulate the blood glucose level. Receptors like GLUT2, PPAR, IR, SGLT1, DPP-IV, GP(18). In this recent research we have chosen two receptors PPARg and Glycogen phosphorylase. In the 1990s, peroxisome proliferation mediators identified as PPARs emerged has been one of the most intensively researched transcription factors(19). Since PPARs control beta cell biology, and alter the pancreatic lipidome, they are a prime choice for this kind of method(20). In PPAR Gamma, Insulin attaches to the insulin receptor, which then mediates its metabolic actions. It interacts with downstream mediators such as IRS-1 and PI3K. PI3K can be activated directly or indirectly, resulting in the creation of PIP3. In insulin signaling transduction, the PI3K/ AKT/GSK-3 signaling pathway is involved, with GSK-3 being regulated and controlled by insulin. AKT activation is also involved in the pathway, which phosphorylates the Ser9 site of GSK-3 and limits its action(21). Glycogen Phosphorylase catalyzes glycogen breakdown to produce glucose-1-P, used by muscle for metabolic energy. Phosphoglucomutase and glucose-6-phosphatase convert glucose in liver to glucose(22). ADME properties allows in the prediction of drug properties such as absorption, distribution, metabolism, and excretion. It helps in selection process of drug discovery process to select a specific organosulphur compounds. Lipinski and colleagues introduced the "Rule of Five" a rule-based filter for drug likeness. It was the first and most well-known rule-based filter of drug a connection distinguishing whether a chemical is orally absorbed whether it works or not(23). It identifies molecule activity based on molecular weight, partition coefficient (log p), hydrogen bond acceptors and hydrogen bond donor. The weight of drug should not exceed more than 500Da, Log p should be less than 5, HBA should be less than10 while HBD should be less than 5 and molar refractivity should be between 40-130(24). If any drug follows these rules, it is effective and safe drug. ADMET properties were calculated by the help of SwissADME. The results are given below in table 2. Toxtree and ADMET SAR are open-source software tool designed for the prediction of toxicological properties of chemical compounds(25). It is particularly focused on predicting the toxicity of chemicals. The results are given below in table 3. PyRx which is an open-source software was used for a molecular docking. PyRx is particularly useful for virtual screening(26). PyRx consist of AutoDock which is integrated in it. Before starting the docking on PyRx make sure to convert the format of a receptor and ligand file into a PDB file. PyRx gives out the Binding affinity and energy of each compound. The results are given below in table 4. Our recent research has focused on identifying a suitable organosulphur compound docking against receptor PPAR Gamma and GP which can act as suitable drug candidate in treatment of diabetes. The results were compared with a standard drug Thiazolidinediones. A molecule with highest binding affinity was chosen and its docking visualization against receptor was done by the help of Discovery studio.

Causes of diabetes

Type 2 diabetes: substantially results from insulin resistance. Insulin resistance happens when cells in your muscles, fat and liver do not respond as they should to insulin. Several factors and conditions contribute to varying degrees of insulin resistance, including bulk, lack of physical exercise, diet, hormonal imbalances, genetics, and certain medicines(27).

Autoimmune disorder: Type 1 diabetes occur when the immune system attacks the insulin-producing cells in your pancreas.

Hormonal imbalances: During gestation, the placenta releases hormones that create insulin resistance. Maternal pancreatic β-cell dysfunction leads to impaired glucose tolerance(28). Other hormonerelated conditions like acromegaly and Cushing syndromes can also produce Type 2 diabetes(29).

Pancreatic damage: Physical damage to your pancreas from a condition, surgery or Injury can impact its capability to make insulin, resulting in Type 3c diabetes(30).

Inheritable mutations: Certain inheritable mutations can lead to neonatal diabetes(31). Long-term use of certain medicines can also lead to Type 2 diabetes, including corticosteroids.

Receptor that plays a crucial part in Diabetes treatment: Metabolically, the insulin receptor plays a crucial part in the regulation of glucose homeostasis; a functional process that under degenerate conditions may lead to a range of clinical personifications including diabetes and cancer(32).

Drugs used in treatment of diabetes

Some of the drugs used in the treatment are Tolbutamide, Glimepiride, Metformin, Rosiglitazone, (33),(34),(35,36),(36). The side-effects of these drugs are given in Table 1.

Use of Ayurveda in treatment of diabetes

1. *Udwartana* is a cream massage frequently used for slimming and treatment of bulkiness that can be done daily.

2. *Dhanyamladhara* is frequently used in Ayurveda to combat adiposity, inflammation, muscular pain, neuropathy, hemiplegia, and rheumatic complaints.

3. *Snehapana* is a process of full body internal and external lubrication via drinking ghee and animal-fat oil as well as massaging the oil on without any other oral input.

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4. ***Abhyanga*** is a warm oil-massage. The oil is frequently premedicated with flavorings for specific conditions.

5. ***Bashpasweda*** is a fume chamber in which the patient sits while fume emanates from a boiling herbal decoction.

6. ***Virechana*** is an alternate procedure in the sequence of Panchakarma (Ayurveda Detoxification Program) that involves using natural medications that have a laxative effect, substantially aimed at reducing pitta dosha and poisonous accumulation in the gastrointestinal tract, liver, and gallbladder(37) .

Computer Aided Drug Designing: Ultra-modern medicine discovery uses computer-aided drug design to find possible medicinal molecules(38). It is presently the stylish option for high-output screening, which is generally employed in medicine development. Ways employed in this approach are used in nearly every position of medicine development. Structure-Based Drug Designing (SBDD), Ligand-Based Drug Designing (LBDD),and Fragment-Based Drug Designing (FBDD) are some of the in-silico medicine design methodologies(39).

Table 1: Drugs used in treatment of diabetes and their side-effects

Name of drug	FDA Approval	Formulation	Dosage	Possible Side Effects
Tolbutamide	1957	500 mg tablets	Taken two or three times daily.	Hypoglycaemia, weight gain.
Glimepiride	1995	1mg, 2mg, 4mg tablets	Taken once daily.	Cardiovascular effect, Hypoglycaemia, weight gain.
Metformin	1994	500 mg, 850 mg, 1000 mg tablets	Taken two or three times daily.	Gastrointestinal symptoms (diarrhoea, nausea), lactic acidosis.
Rosiglitazone	1999	2mg, 4mg, 8mg tablets	Taken once or twice daily.	Anaemia, bone loss, fractures in women.
Glyburide, micronized	1992	1.5 mg, 3 mg,4.5 mg, 6 mg micronized tablets	Taken once or twice (if >6 mg) daily.	Hypoglycemia, weight gain.

Aims, objectives and Methods

The study aims to identify potential antidiabetic organosulfur compounds through in silico molecular docking against PPAR-γ and Glycogen Phosphorylase receptors. In the present study, bio informatics tools like PubChem, Protein Data Bank, SwissADME, Toxtree, ADMET SAR, PyRx, Biovia Discovery Studio Visualizer, Chemsketch and Marvin were used.

Figure 1: 3D Structure of PPARG

Figure 2: ERRAT Quality Analysis of PPARG

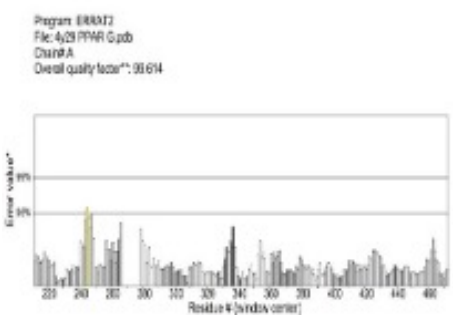


Figure 3: Ramchandran Plot for PPARG

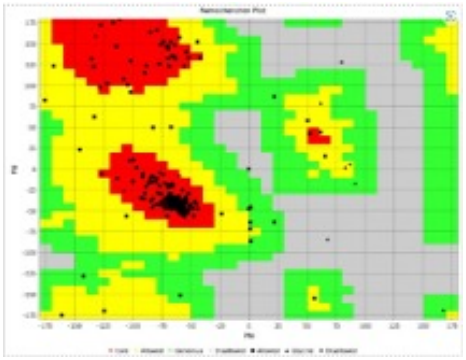


Figure 4: 3D Structure of GP

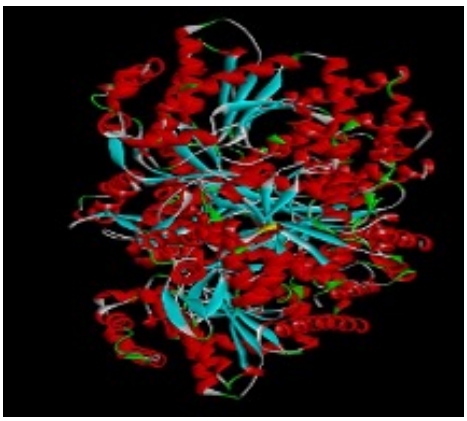


Fig 5. ERRAT Quality Analysis of GP

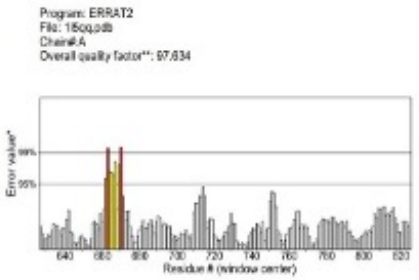
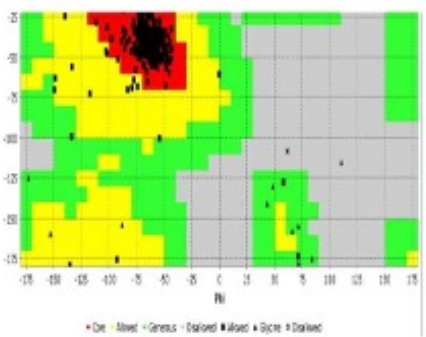


Fig 6. Ramchandran Plot for GP



Preparation of Protein

Protein Data Bank was used to retrieve the 3D structure of the target protein receptor PPAR-**γ** and Glycogen Phosphorylase having a resolution length up to 1.5 to 2 Å and downloaded in PDB format. Discovery Studio Visualizer was utilized to remove water molecules from the protein structure. The quality and error were analyzed using Errat online server. The distribution of the Ψ and ϕ of amino acids residual in protein was observed under the Ramachandran Plot.

Ramachandran plot is a graphical representation of the phi (ϕ) and psi (ψ) angles of amino acid residues in a protein. It hives a detailed view about the torsion angles of a protein structure.

- **Red Color:** Residues in the most favored region. This indicates that the combination of phi and psi angles for these residues is energetically favorable and commonly observed in stable protein structures.
- **Yellow Color:** Residues in the additionally allowed region. These residues have torsion angles that are less common but still permissible in protein structures. They are somewhat less favored than those in the most favored region.
- **Faint Yellow:** Residues in the generously allowed region. Similar to the additionally allowed region, these residues have torsion angles that are less common but are still considered acceptable. However, they are less favorable than both the most favored and additionally allowed regions.
- **Grey Color:** Residues in the disallowed region. This indicates that the combination of phi and psi angles for these residues is energetically unfavorable or structurally implausible. Proteins with residues in this region may be distorted or have an incorrect conformation.

Selection and Preparation of Ligand

The structure of the organosulphur-based functional chemicals found in plants was retrieved from PubChem. Selection was based on Lipinski's rule of five, ADMET properties, and docking scores.The study retrieved 22 organosulfur compounds from PubChem. SMILES was used as an input for each ligand to calculate the physicochemical properties as well as similarity search by using chemicalize.

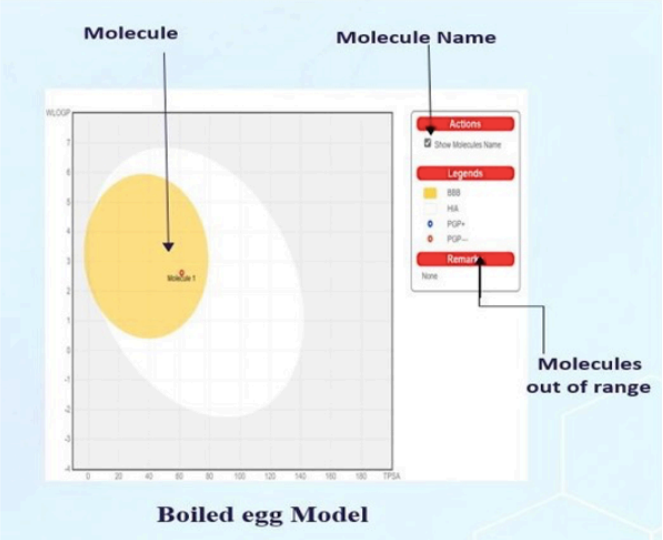
Prediction of ADME characteristics using SwissADME

The Swiss ADME online web tool was employed for the comprehensive screening of bioavailability and pharmacokinetic characteristics, encompassing parameters related to absorption, distribution, metabolism, and excretion (ADME). The chosen ligands were represented using SMILES Notation in the form of an input file, which was then organized and tabulated in spreadsheets or Excel to generate a list, with each molecule having its designated entry.

SwissADME Tool

In the initial stages of drug discovery, anticipating absorption, distribution, metabolism, and excretion (ADME) characteristics helps mitigate the risks associated with pharmacokinetic failures. The pioneering work of Lipinski et al. involved the examination of compounds that are orally active to establish physicochemical ranges indicative of high oral drug probability, commonly referred to as drug-likeness(40). Integrated into the Swiss Drug Design workspace, SwissADME provides seamless interoperability, granting users access to various CADD tools developed by the Molecular Modelling Group of the SIB Swiss Institute of Bioinformatics. These tools include ligand-based virtual screening (Swiss Similarity), bio target prediction (Swiss Target Prediction), molecular docking (Swiss Dock), and bioisosteric design (Swiss Bioisostere).

Fig 7. Boiled egg model from SwissADME



ADME Studies

ADME encompasses the processes governing the nature and delivery of pharmaceutical compounds within an organism, with a particular focus on the human body. Poor pharmacokinetics is a primary cause of drug development failure. Employing a Pharmacokinetic (PK) model becomes crucial to ascertain the optimal dose and dosing interval, thereby minimizing the risk of undesired administration and side effects. By merely using a molecule structure, in silico models are a simple and economical way to estimate ADME features.

The Lipinski's rule of five is the most important model to check the pharmacological properties of compounds(41). The Lipinski rule is as follows:

- MW <500 Da; Log Pw oct <5;
- no more than 5 hydrogen bond donors;
- no more than 10 hydrogen bond acceptors.

Different parameters for predicting ADME properties are:

- **Lipophilicity:** Lipophilicity, a critical physicochemical property in pharmacokinetics and drug development, is quantified through the partition coefficient between n-octanol and water, denoted as log Po/w. Recognizing the significance of this parameter, SwissADME incorporates a dedicated

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section. Within SwissADME, users can freely utilize five XLOGP329 prediction models.

- **Water Solubility:** With the convenience of handling and formulation as a priority, having a resolvable molecule considerably improves the process of discovering new drug candidates. It is critical to evaluate the solubility of medications that are intended for oral delivery. To provide a significant quantity of active components in a small volume, the medicine for parenteral use must be highly soluble in water. For parenterally administered medications, high water solubility is crucial to ensure the delivery of a substantial quantity of active components within a limited volume.

- **Pharmacokinetics:** The prediction of skin permeability coefficient (Kp) is a function within PK models. A lower log Kp (cm/s) signifies reduced permeability of the molecule through the skin. The BOILED-EGG model's readout is utilized to forecast passive human HIA and penetration through BBB. Approximately 90 percent of therapeutic compounds, as reported by various authors, are substrates for five principal isoforms (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4). Several CYP isoform inhibitors have been discovered. Some have diverse effects on different CYP isoforms, whereas others are selective for certain isoenzymes50.

- **Drug Likeness:** This assessment gauges the potential of a chemical to serve as an oral medication with regards to bioavailability. The initial application of the rule of five was introduced through the Lipinski (Pfizer) filter. The procedures of Ghose (Amgen), Veber (GSK), Egan (Pharmacia), and Muegge (Bayer) were all adopted from other sources. Generally, any deviation from the Lipinski rule is deemed unacceptable, barring rare circumstances.

Drug Score and Toxicity Study

Utilizing the OSIRIS property explorer program to simulate for solubility, drug ratings, and toxicity estimates(42). Toxtree predicts and determines the taxological approach in tree- based approach while Admet SAR is user friendly interface to search for studies(43).

Molecular Docking

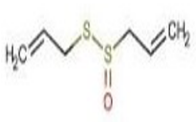
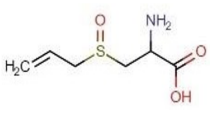
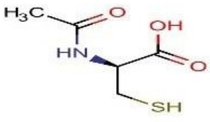
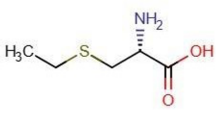
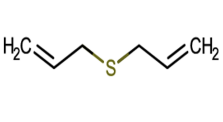
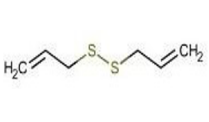
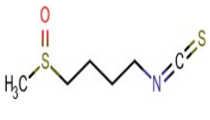
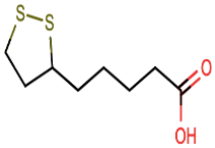
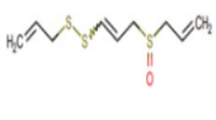
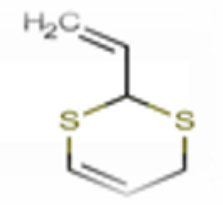
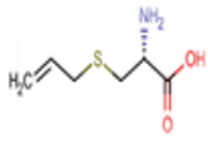
The exploration of the interaction between two or more molecular structures, such as a drug and an enzyme or protein, is referred to as molecular docking. Molecular docking is a molecular modelling technique designed to forecast the interactions of small compounds with proteins. This method enables the simulation of atomic-level interactions connecting a small chemical and a protein. The docking process involves predicting the structure of the ligand, its position and orientation within binding sites, and measuring binding affinity. Various docking techniques are employed, including stiff ligand and stiff receptor docking, flexible ligand and stiff receptor docking, and flexible ligand and flexible receptor docking. Blind docking and site-specific docking are two different ways to dock. When no information about the protein's binding sites is available, blind docking is used.

PyRx:

Molecular docking was performed by using PyRx which is a virtual screening for computational drug discovery. It provides facility of multiple ligands docking. Loaded the protein molecule from file as PDB and convert it into PDB - qt by selecting auto doc which make macromolecule. Using an open babble, inserted one-by-one ligands from the file as it showed molecular weight, number of atoms, and formulae. PyRx is quite easy to use as it is automatically analyzed the interactions. The binding affinity of each ligand were saved in Excel sheet.

Compounds used in the process of molecular docking are as follows:

Table 2: 2D Structure of Compounds

Allicin	Alliin	Acetyl cysteine	S-ethyl cysteine	Diallyl sulfide	Diallyl disulfide
					
Sulforaphane	Lipoic Acid	Ajoene	Allyl Propyl Disulfide	2-Vinyl-4H-1,3-dithiine	S-allyl-L-cysteine
					
Allixin	Vasicine	Allylmercapto-cysteine	Pentafluorobutane	Cinnamonitrile	Thymoquinone

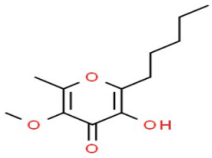
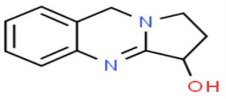
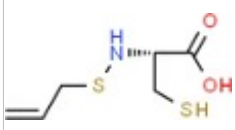
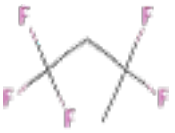
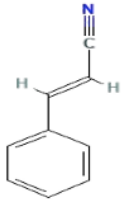
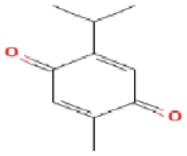
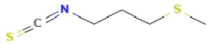
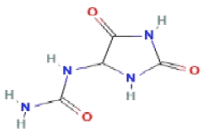
					
	Isothiocyanates	Allantoin	Furfuryl Thioacetate	Trimethyl-bicyclo-heptane	
					

Table 3: Physical parameters and Physiochemical Properties

Ligand	Molecular Formula		Molar mass (gmol-1)	LogP value	Hydrogen Bond Donors (HBD)	Hydrogen Bond Acceptors (HBA)	Refractivity (Cm^3/mol)
1	C6H10OS2	$C_6H_{10}OS_2$	162.3	2.021	0	1	44.93
2	C6H11NO3S	$C_6H_{11}NO_3S$	177.22	-3.741	2	4	43.72
3	C5H9NO3S	$C_5H_9NO_3S$	163.20	-0.711	3	3	37.67
4	C5H11NO2S	$C_5H_{11}NO_2S$	149.21	-2.151	2	3	37.67
5	C6H10S	$C_6H_{10}S$	114.21	2.479	0	0	37.32
6	C6H10S2	$C_6H_{10}S_2$	146.3	2.761	0	0	45.42
7	C6H11NOS2	$C_6H_{11}NOS_2$	177.3	0.22	0	2	49.57
8	C8H14O2S2	$C_8H_{14}O_2S2$	206.32	2.114	1	2	54.37
9	C9H14OS3	$C_9H_{14}OS_3$	234.4	3.08	0	1	68.1
10	C6H12S2	$C_6H_{12}S_2$	148.29	2.909	0	0	45.53
11	C6H8S2	$C_6H_8S_2$	144.25	2.374	0	0	43.22
12	C6H11NO2S	$C_6H_{11}NO_2S$	161.22	-1.777	2	3	42.09
13	C12H18O4	$C_{12}H_{18}O_4$	226.26	2.74	1	4	59.6
14	C11H12N2O	$C_{11}H_{12}N_2O$	188.22	1.31	1	3	53.5
15	C6H11NO2S2	$C_6H_{11}NO_2S_2$	193.28	2.48	2	3	50.6
16	C10H12O2	$C_{10}H_{12}O_2$	164.20	1.99	0	2	47.52
17	C9H7N	C_9H_7N	129.16	1.82	0	1	41.09
18	C7H8O2S	$C_7H_8O_2S$	156.20	1.97	0	2	41.08
19	C6H10S3	$C_6H_{10}S_3$	178.34	2.65	0	0	52.78
20	C4F4H5S	$C_4F_4H_5S$	180.14	1.62	0	5	29.60
21	C11H18O	$C_{11}H_{18}O$	166.26	2.47	1	1	51.19
22	C10H16O	$C_{10}H_{16}O$	152.23	2.12	0	1	45.64

Table 4: Prediction of ADMET Properties for selected ligands

No	TPSA	Log Kp	Consensus Log P	BBB Permeatio	GI adsorptio	CYP1A2 inhibitor	CYP2C19	CYP2C9 inhibitor	CYP2D6	CYP3A4	P-gp substrat
1	61.58	-6.36	1.61	Yes	High	No	No	No	No	No	No
2	91.7	-7.25	0.27	N0	High	No	No	No	No	No	No
3	105.2	-7.04	-0.08	No	High	No	No	No	No	No	No
4	88.62	-8.88	-0.68	No	High	No	No	No	No	No	No
5	25.3	-5.46	2.14	Yes	High	No	No	No	No	No	No
6	50.6	-5.63	2.39	Yes	High	No	No	No	No	No	No
7	80.73	-6.38	1.93	No	High	No	No	No	No	No	No
8	87.9	-6.37	2.04	No	High	No	No	No	No	No	No
9	86.88	-6.52	2.52	No	High	No	No	Yes	No	No	No
10	50.6	-5.47	2.52	Yes	High	No	No	No	No	No	No
11	50.6	-5.55	2.22	Yes	High	No	No	No	No	No	No
12	88.62	-8.75	-0.45	No	High	No	No	No	No	No	No
13	59.67	-5.71	2.38	Yes	High	Yes	Yes	No	No	No	No
14	35.83	-7.14	1.17	No	High	No	No	No	No	No	Yes
15	113.43	-8.53	-0.09	No	High	No	No	No	No	No	No
16	61.58	-6.36	1.61	Yes	High	No	No	No	No	No	No

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17	113.32	-8.81	-1.85	No	Low	No	No	No	No	No	No
18	88.62	-8.75	-0.45	No	High	No	No	No	No	No	No
19	34.14	-5.74	1.85	Yes	High	No	No	No	No	No	No
20	17.7	-5.67	2.37	Yes	High	No	No	No	No	No	No
21	75.9	-5.51	2.68	Yes	High	No	No	No	No	No	No
22	38.8	-5.51	2.89	Yes	High	No	No	No	No	No	No

Table 5: Additional Parameters of the selected compounds

No	Log S	Drug Likeness	Drug Score	Eye Irritation	Eye corrosion	Skin sensitization	Crammers Rule	Carcinogenicity	Hepatotoxicity	Nephrotoxicity
1	-1.22	-6.13	0.48	Positive	Positive	Negative	High Class	Positive	Positive	Positive
2	-0.14	-10.7	0.49	Negative	Negative	Negative	High Class	Negative	Positive	Negative
3	-1.26	-13.06	0.49	Positive	Negative	Negative	High Class	Negative	Positive	Negative
4	-1.01	-6.24	0.49	Negative	Negative	Negative	High Class	Positive	Positive	Negative
5	-2.01	-3.93	0.29	Positive	Positive	Positive	High Class	Positive	Positive	Positive
6	-2.71	-4.7	0.45	Positive	Positive	Positive	High Class	Positive	Positive	Positive
7	-1.25	-6.47	0.25	Positive	Negative	Negative	High Class	Positive	Negative	Positive
8	-2.86	-9.44	0.27	Positive	Negative	Negative	High Class	Negative	Positive	Negative
9	-2.45	-5.8	0.46	Positive	Positive	Negative	High Class	Positive	Positive	Positive
10	-2.77	-5.03	0.44	Positive	Positive	Positive	High Class	Positive	Positive	Positive
11	-2.07	-2.34	0.51	Positive	Positive	Positive	High Class	Negative	Positive	Positive
12	-1.22	-8.97	0.49	Positive	Negative	Negative	High Class	Negative	Positive	Negative
13	-1.29	-5.45	0.38	Positive	Negative	Negative	High Class	Negative	Negative	Negative
14	-2.35	-4.6	0.41	Positive	Negative	Negative	High Class	Negative	Positive	Negative
15	-2.65	-3.76	0.27	Positive	Negative	Negative	High Class	Negative	Negative	Negative
16	-2.25	-1.14	0.21	Positive	Positive	Positive	High Class	Positive	Positive	Positive
17	-1.77	-1.3	0.25	Positive	Positive	Positive	High Class	Positive	Positive	Positive
18	-2.18	-1.5	0.23	Positive	Positive	Positive	High Class	Positive	Positive	Positive
19	-2.21	-3.90	0.29	Positive	Positive	Positive	High Class	Positive	Positive	Positive
20	-2.16	-3.1	0.30	Positive	Negative	Positive	High Class	Positive	Positive	Positive
21	0.68	9.5	0.27	Positive	Negative	Negative	High Class	Negative	Positive	Positive
22	-2.43	-8.53	0.26	Positive	Positive	Negative	High Class	Negative	Positive	Positive

Table 6: Docking Results with Receptor PPARG

Sr.no	Ligand Name	Molecular formula	Binding affinity
1	Allicin	$C_6H_{10}OS_2$	-3.4
2	Alliin	$C_6H_{11}NO_3S$	-4.7
3	Acetyl cysteine	$C_5H_9NO_3S$	-4
4	S-ethyl cysteine	$C_5H_{11}NO_2S$	-4.2
5	diallyl sulfide	$C_6H_{10}S$	-2.9
6	diallyl disulfide	$C_6H_{10}S_2$	-3.1
7	Sulforaphane	$C_6H_{11}NOS_2$	-3.7
8	Lipoic Acid	$C_8H_{14}O_2S2$	-4.7
9	Ajoene	$C_9H_{14}OS_3$	-4.7
10	Allyl Propyl Disulfide	$C_6H_{12}S_2$	-2.9
11	2-Vinyl-4H-1,3-dithiine	$C_6H_8S_2$	-3.5
12	S-allyl-L-cysteine	$C_6H_{11}NO_2S$	-4.1
13	Allixin	$C_{12}H_{18}O_4$	-5.7
14	Vasicine	$C_{11}H_{12}N_2O$	-6.5
15	Allyl-mercapto-cysteine	$C_6H_{11}NO_2S_2$	-4.9
16	Thymoquinone	$C_{10}H_{12}O_2$	-5.8
17	Cinnamonitrile	C_9H_7N	-5.9
18	Allantoin	$C_4H_6N_4O_3$	-5.5
19	Isothiocyanate	C_7H_5NS	-5.9
20	Dially Trisulfate	$C_6H_{10}S_3$	-5.1
21	Pentafluorobutane	$C_4F_4H_5S$	-4.8
22	Nopol Oxide	$C_{11}H_{18}O$	-4.6
23	Thiazolidinediones	$C_{18}H_{19}N_3O_3S$	-7.9

Table 7: Docking Results with Receptor GP

Sr.no	Ligand Name	Molecular formula	Binding affinity
1	Allicin	$C_6H_{10}OS_2$	-4.6
2	Alliin	$C_6H_{11}NO_3S$	-4.6
3	Acetyl cysteine	$C_5H_9NO_3S$	-4.5
4	S-ethyl cysteine	$C_5H_{11}NO_2S$	-4.6
5	diallyl sulfide	$C_6H_{10}S$	-3.9
6	diallyl disulfide	$C_6H_{10}S_2$	-3.5
7	Sulforaphane	$C_6H_{11}NOS_2$	-3.5
8	Lipoic Acid	$C_8H_{14}O_2S2$	-4.5
9	Ajoene	$C_9H_{14}OS_3$	-4.6
10	Allyl Propyl Disulfide	$C_6H_{12}S_2$	-4.1
11	2-Vinyl-4H-1,3-dithiine	$C_6H_8S_2$	-4.5
12	S-allyl-L-cysteine	$C_6H_{11}NO_2S$	-4.8
13	Allixin	$C_{12}H_{18}O_4$	-6.6
14	Vasicine	$C_{11}H_{12}N_2O$	-6
15	Allyl-mercapto-cysteine	$C_6H_{11}NO_2S_2$	-4.6
16	Thymoquinone	$C_{10}H_{12}O_2$	-5.6
17	Cinnamonitrile	C_9H_7N	-5.2
18	Allantoin	$C_4H_6N_4O_3$	-5.5
19	Isothiocyanate	C_7H_5NS	-5.9
20	Dially Trisulfate	$C_6H_{10}S_3$	-4.8
21	Pentafluorobutane	$C_4F_4H_5S$	-3.9
22	Nopol Oxide	$C_{11}H_{18}O$	-5.1
23	Thiazolidinediones	$C_{18}H_{19}N_3O_3S$	-7

Results and Discussion

The analysis and outcomes of the screened compounds demonstrated compliance with Lipinski's rule of five, stipulating that molecular weight should not exceed 500 Da, Log P value should be less than or equal to 5, hydrogen bonding donors should not surpass 5, and the number of hydrogen bonding acceptors should be no more than 10. Deviations in these values may significantly reduce absorption rates. surpass 5, and the number of hydrogen bonding acceptors should be no more than 10. Deviations in these values may significantly reduce absorption rates. The bioavailability related to lipophilicity (log P) indicates the importance of appropriate balance between solubility and permeability.

A substance does not qualify as drug-like if its drug score is zero or lower; on the other hand, if the score is higher than zero, the substance is called a drug. From the screened compounds,every one of the molecules has a drug score above zero. A total polar surface area (TPSA) below 150 Å demonstrates greater polarity, correlating with favorable oral absorption and membrane penetration.

A log Kp value exceeding -2.5 signifies low skin permeability, while values ranging between -5.46 to -8.88 indicate high skin permeability. Resistance to multiple drugs in malignancies can arise from the excessive expression of P-glycoprotein (P-gp) substrates in tumor cells. Among the screened compounds, only one is identified as a P-gp substrate. Ajoene acts as an inhibitor of CYP2C9, while Allixin inhibits CYP1A2 and CYP2C19, suggesting potential liver metabolism.

To assess drug viability, it is crucial to determine the drug's solubility (log S), a key factor influencing dissolution in the gastrointestinal tract and crossing the blood-brain barrier. For effective absorption, the log S value should be greater than -6, and all compounds exhibit significant values.

Various toxicity factors, such as crammers' rule, nephrotoxicity, carcinogenicity, and hepatoxicity, have been examined. A Out of 22 compounds, 10 showed carcinogenecity and 8 showed hepatotoxicity with a negative probability,including allixin and vasicine under toxicity prediction. comprehensive metric, known as the drug score, is employed to assess a compound's approval potential, in consideration with cLogP, drug likeness, molecular weight, LogS and toxicity risks.

Vasicine with PPAR and Allixin with GP have strong binding affinity with standard Thiazolidinediones.

LEU A435, LEU A:436, THR A:440, MET A:439, and VAL A:390 are the amino acid residues surrounding by the Vasicine molecule in its two-dimensional interaction with the PPAR receptor. The green line represents the interaction between of a conventional hydrogen bond with residues LEU A:435 and LEU A:436. Moreover, an unfavourable bump and Pi-sulphur were depicted by the red and green lines.

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Fig.8 2D Interaction of Ligand Vasicine with receptor PPARG

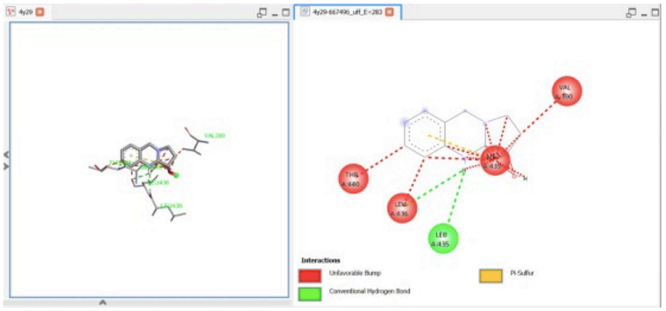
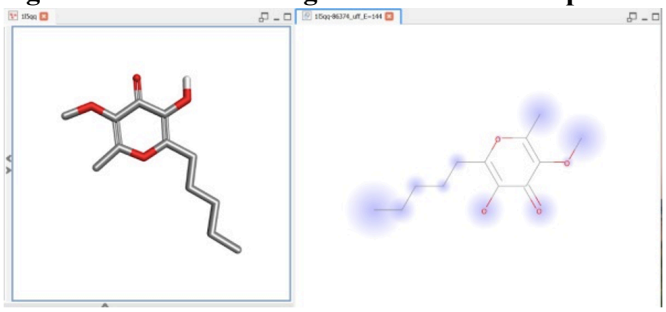


Fig. 9 2D Interaction of ligand Allixin with receptor GP



Conclusion

Diabetes, an intricate metabolic disorder, is influenced by a multitude of factors. Recent insights into the pathogenesis of diabetes have unveiled novel pathways and factors that significantly contribute to the development and progression of the disease. The prominent conditions of resistance to insulin and dysfunction of the β-cell play a substantial part in the aggressiveness of diabetes. In silico approaches using molecular docking have identified druggable and nontoxic organosulfur compounds.

These compounds can be used in wet lab studies and could potentially act as antidiabetic agents in diabetes therapy. Toxicity prediction showed no risk and medium risk. Activation of GPR119 can have several effects that make it potentially effective in managing type 2 diabetes. Some of the helpful effects are insulin secretion, increased hormone release, improved glucose control and appetite regulation.

Although combination therapy for Type 2 Diabetes Mellitus (T2DM) has demonstrated improved health outcomes, it introduces potential complications that necessitate careful consideration. The imperative need for increased attention to emerging comorbidities associated with diabetes is underscored. A multitargeting strategy emerges as a promising approach for T2DM treatment, simultaneously addressing multiple pathways. The primary obstacle in treating T2DM lies in the inadequacy of single target approaches.

Future Scope

T2DM is categorized by resistance to insulin and the inadequacy of β-cell to compensate sufficiently. Consequently, animal models of T2DM often encompass models of insulin resistance and/or β-cell failure. Many rat models of T2DM are obese, mirroring the human condition where rotundity is closely linked to the development of T2DM.

Given the close association between type 2 diabetes and rotundity, most current animal models for type 2 diabetes involve rotundity. Rotundity can result from naturally happening mutations or manipulation of genetics. Additionally, it can be induced through a high-fat diet. Although human rotundity is seldom caused by a single genetic mutation, monogenic models of rotundity are frequently utilized in T2DM research. The most widely used monogenic models of obesity are characterized by defects in leptin signaling.

Transitioning from molecular docking studies to testing on rat models represents a crucial step in this project. It involves determining drug mechanisms for diabetes and identifying appropriate dose levels. Insights from rat model responses may reveal novel therapeutic targets. This step is extremely important as it helps to understand how the drugs may benefit the society.

The most suitable rat model for this purpose is the Obese Diabetic Mice as they develop obesity, exhibit glucose intolerance, and demonstrate insulin resistance.

Conflict of Interest: - No potential conflict of interests declared.

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References

1. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of Type 2 Diabetes Mellitus. Int J Mol Sci. 2020 Aug 30;21(17):6275.
2. Olokoba AB, Obateru OA, Olokoba LB. Type 2 Diabetes Mellitus: A Review of Current Trends.
3. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends. J Epidemiol Glob Health. 2020 Mar;10(1):107–11.
4. GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2023 Jul 15;402(10397):203–34.
5. Padhi S, Nayak AK, Behera A. Type II diabetes mellitus: a review on recent drug based therapeutics. Vol. 131, Biomedicine and Pharmacotherapy. Elsevier Masson SAS; 2020.
6. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. Lancet. 2018 Jun 16;391(10138):2449–62.
7. Ahmad E, Lim S, Lamptey R, Webb DR, Davies MJ. Type 2 diabetes. The Lancet. 2022 Nov;400(10365):1803–20.
8. Modzelewski R, Stefanowicz-Rutkowska MM, Matuszewski W, Bandurska-Stankiewicz EM. Gestational Diabetes Mellitus-Recent Literature Review. J Clin Med. 2022 Sep 28;11(19).

9. Plows JF, Stanley JL, Baker PN, Reynolds CM, Vickers MH. The Pathophysiology of Gestational Diabetes Mellitus. Int J Mol Sci. 2018 Oct 26;19(11).
10. Tuso P. Prediabetes and lifestyle modification: time to prevent a preventable disease. Perm J. 2014;18(3):88–93.
11. 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 anti-diabetic activity. Biomolecules. 2021 Nov 1;11(11).
12. Dal Canto E, Ceriello A, Rydén L, Ferrini M, Hansen TB, Schnell O, et al. Diabetes as a cardiovascular risk factor: An overview of global trends of macro and micro vascular complications. Eur J Prev Cardiol. 2019 Dec 1;26(2_suppl):25–32.
13. Kumar M, Kaushik D, Kaur J, Proestos C, Oz F, Oz E, et al. A Critical Review on Obesity: Herbal Approach, Bioactive Compounds, and Their Mechanism. Vol. 12, Applied Sciences (Switzerland). MDPI; 2022.
14. Walag AMP, Ahmed O, Jeevanandam J, Akram M, Ephraim-Emmanuel BC, Egbuna C, et al. Health Benefits of Organosulfur Compounds. In: Functional Foods and Nutraceuticals. Cham: Springer International Publishing; 2020. p. 445–72.
15. Pareek S, Sagar N, Sharma S, Kumar V. Onion (Allium cepa L.). In 2017. p. 1145-1161 (16).
16. Zhao XX, Lin FJ, Li H, Li HB, Wu DT, Geng F, et al. Recent Advances in Bioactive Compounds, Health Functions, and Safety Concerns of Onion (Allium cepa L.). Front Nutr. 2021;8:669805.
17. Omar SH, Al-Wabel NA. Organosulfur compounds and possible mechanism of garlic in cancer. Saudi Pharm J. 2010 Jan;18(1):51–8.
18. Arif R, Ahmad S, Mustafa G, Mahrosh HS, Ali M, Tahir ul Qamar M, et al. Molecular Docking and Simulation Studies of Antidiabetic Agents Devised from Hypoglycemic Polypeptide-P of Momordica charantia. Biomed Res Int. 2021 Sep 17;2021:1–15.
19. Ballav S, Biswas B, Sahu VK, Ranjan A, Basu S. PPAR-γ Partial Agonists in Disease-Fate Decision with Special Reference to Cancer. Cells. 2022 Oct 13;11(20):3215.
20. Holm LJ, Mønsted MØ, Haupt-Jorgensen M, Buschard K. PPARs and the development of type 1 diabetes. Vol. 2020, PPAR Research. Hindawi Limited; 2020.
21. Arneth B, Arneth R, Shams M. Metabolomics of Type 1 and Type 2 Diabetes. Int J Mol Sci. 2019 May 18;20(10).
22. Oikonomakos N. Glycogen Phosphorylase as a Molecular Target for Type 2 Diabetes Therapy. Curr Protein Pept Sci. 2002 Dec 1;3(6):561–86.
23. Guan L, Yang H, Cai Y, Sun L, Di P, Li W, et al. ADMET-score – a comprehensive scoring function for evaluation of chemical drug-likeness. Medchemcomm. 2019;10(1):148–57.
24. Benet LZ, Hosey CM, Ursu O, Oprea TI. BDDCS, the Rule of 5 and drugability. Adv Drug Deliv Rev. 2016 Jun 1;101:89–98.
25. Cheng F, Li W, Zhou Y, Shen J, Wu Z, Liu G, et al. admetSAR: A Comprehensive Source and Free Tool for Assessment of Chemical ADMET Properties. J Chem Inf Model. 2012 Nov 26;52(11):3099–105.
26. Dallakyan S, Olson AJ. Small-Molecule Library Screening by Docking with PyRx. In 2015. p. 243–50.
27. Wu Y, Ding Y, Tanaka Y, Zhang W. Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. Int J Med Sci. 2014;11(11):1185–200.
28. Alejandro EU, Mamerto TP, Chung G, Villavieja A, Gaus NL, Morgan E, et al. Gestational Diabetes Mellitus: A Harbinger of the Vicious Cycle of Diabetes. Int J Mol Sci. 2020 Jul 15;21(14).
29. Popoviciu MS, Paduraru L, Nutas RM, Ujoc AM, Yahya G, Metwally K, et al. Diabetes Mellitus Secondary to Endocrine Diseases: An Update of Diagnostic and Treatment Particularities. Int J Mol Sci. 2023 Aug 11;24(16).
30. Hardt PD, Brendel MD, Kloer HU, Bretzel RG. Is Pancreatic Diabetes (Type 3c Diabetes) Underdiagnosed and Misdiagnosed? Diabetes Care. 2008 Feb 1;31(Supplement_2):S165–9.
31. Støy J, Edghill EL, Flanagan SE, Ye H, Paz VP, Pluzhnikov A, et al. Insulin gene mutations as a cause of permanent neonatal diabetes. Proceedings of the National Academy of Sciences. 2007 Sep 18;104(38):15040–4.
32. Zhang X, Zhu X, Bi X, Huang J, Zhou L. The Insulin Receptor: An Important Target for the Development of Novel Medicines and Pesticides. Int J Mol Sci. 2022 Jul 14;23(14).
33. Kenneth R. Feingold 1 Kenneth R Feingold 1 BA 2, MRB 3, AB 4, GC 5, EC 6, WW de H. Oral and Injectable (Non-Insulin) Pharmacological Agents for the Treatment of Type 2 Diabetes.
34. Kumar R. Evolution of tolbutamide in the Treatment of diabetes mellitus. Journal of Medical Pharmaceutical and Allied Sciences. 2020 Dec 15;9(6):2605–9.
35. Basit A, Riaz M, Fawwad A. Glimepiride: evidence-based facts, trends, and observations (GIFTS). [corrected]. Vasc Health Risk Manag. 2012;8:463–72.
36. Shurrab NT, Arafa ESA. Metformin: A review of its therapeutic efficacy and adverse effects. Obes Med. 2020 Mar;17:100186.
37. Gordon A, Buch Z, Baute V, Coeytaux R. Use of Ayurveda in the Treatment of Type 2 Diabetes Mellitus. Glob Adv Health Med. 2019 Jan 7;8:216495611986109.
38. Macalino SJY, Gosu V, Hong S, Choi S. Role of computer-aided drug design in modern drug discovery. Arch Pharm Res. 2015 Sep 25;38(9):1686–701.
39. Surabhi S, Singh B. COMPUTER AIDED DRUG DESIGN: AN OVERVIEW. Journal of Drug Delivery and Therapeutics. 2018 Sep 18;8(5):504–9.
40. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-

likeness and medicinal chemistry friendliness of small molecules. Sci Rep. 2017 Mar 3;7:42717.
41. Shin HK, Kang YM, No KT. Predicting ADME Properties of Chemicals. In: Handbook of Computational Chemistry. Dordrecht: Springer Netherlands; 2016. p. 1–37.
42. Rajalakshmi R, Lalitha P, Sharma SC, Rajiv A, Chithambharan A, Ponnusamy A. *In silico* studies: Physicochemical properties, drug score, toxicity predictions and molecular docking of organosulphur compounds against *Diabetes mellitus*. Journal of Molecular Recognition. 2021 Nov 24;34(11).
43. Contrera JF. Validation of Toxtree and SciQSAR in silico predictive software using a publicly available benchmark mutagenicity database and their applicability for the qualification of impurities in pharmaceuticals. Regul Toxicol Pharmacol. 2013 Nov;67(2):285–93.

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