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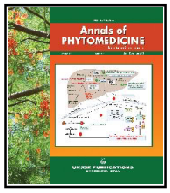

Original Article : Open Access

In silico molecular docking analysis of potential antidiabetic phytochemicals from *Ocimum sanctum* L. against therapeutic targets of type 2 diabetes

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Abstract

Ocimum sanctum L. is a plant used for centuries in alternative medicine to treat diabetes. A review of the scientific literature shows that it has numerous pharmacological effects, including those of antidiabetic, antioxidant, antimicrobial, antifungal, antiallergic, antiviral, and anticancer agents. This research aimed to determine the molecular basis of antidiabetic activities by identifying novel plant-derived antidiabetic metabolites from *O. sanctum*. The phytochemical library of *O. sanctum* was mined from the literature review. Protein data bank is used to get structural models of therapeutic target proteins (SGLT2 and PPAR-γ). AutoDock is used to virtually screen an *O. sanctum* phytochemical library against two therapeutic targets of diabetes. After that molinspiration tool, DruLiTo, admetSAR and SwissADME were used for drug-likeness prediction for the top ten screened phytochemicals. FDA-approved drugs for diabetes (bexagliflozin and ertugliflozin) were used as a control for ADMET studies. Using Ligplot software, the 2D interactions of the complex protein-ligand structure (including hydrogen bonds and bond length) were also analyzed. Alpha-carotene, verbenone, spathulenol, (-)-globulol, and alpha-selinene were identified as promising antidiabetic agents by docking scores (binding energy), drug-likeness, and ADMET studies. Our research indicates that *O. sanctum* compounds are highly promising antidiabetic possibilities. Utilizing contemporary technology, these compounds could be utilized to create effective antidiabetic medications from a natural resource.

1. Introduction

Type 2 diabetes, also known as diabetes mellitus, is a chronic metabolic condition characterized by elevated glucose levels in the bloodstream and inadequate production and effectiveness of insulin. This condition ranks as the seventh leading contributor to worldwide mortality (Maritim *et al*., 2003; Thent and Latiff, 2018). Type 2 diabetes (T2D) is a chronic condition responsible for 4.2 million fatalities and an additional 760 million U.S. dollars in healthcare costs worldwide in 2019 (Diabetes Atlas). Approximately 1.5 million fatalities yearly are attributed to D.M. (Nde *et al*., 2022). The latest data from the International Diabetes Federation (IDF) reveals that approximately 463 million adults aged 20 to 79, have diabetes, mainly in low- and middle-income nations. Predictions indicate this number could surge to 700 million by 2045 (Diabetes Atlas). Studies have indicated that people with diabetes mellitus have lower antioxidant levels and produce more free radicals. The source of oxidative stress arises from a disparity between the generation of oxygen-derived radicals and the antioxidant mechanism. This phenomenon is evident in both types of diabetes mellitus (Bacanli *et al*., 2019). Jyoti and her colleagues (2022) explored how underutilized brassica seed meals could serve as a reservoir of natural antioxidants, potentially contributing to their ability to facilitate antidiabetic effects. Failure to address the management of prolonged outcomes may result in retinopathy, nephropathy, atherosclerosis, and sexual dysfunction, as indicated by the American Diabetes Association (2005) and Lankatillake *et al*. (2019).

Optimal health is a fundamental driver of overall wellness and acts as a bulwark against enduring ailments such as cancer, diabetes, elevated cholesterol, oxidative stress, and inflammation. Varied spices contain bioactive compounds favourably correlate with chronic conditions, demonstrating remarkable efficacy in thwarting cancer, cardiovascular issues, diabetes, inflammation, cholesterol imbalances, microbial infections, and more (Rani *et al*., 2023). From a scientific vantage, the indigenous fruits of India harbour substantial potential in mitigating diverse maladies. Predominantly, these fruits are imbued with essential constituents like sugars, carbohydrates, proteins, amino acids, flavonoids, polyphenols, vitamins, minerals, steroids, alkaloids, and terpenes (Chellammal, 2022). The antidiabetic potential of phytochemicals has been the subject of extensive research, with many exhibiting promising results in preclinical and clinical studies. Studies have demonstrated, for instance, that phytochemicals such as berberine, curcumin, and resveratrol have the potential to lower blood glucose levels, enhance insulin sensitivity, and reduce the risk of diabetic complications (Panahi *et al*., 2017).

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Due to its significant pharmacological activities, *O. sanctum*, also known as sacred basil, has been traditionally employed in Ayurvedic medicine to treat various ailments. *O. sanctum* has numerous biological properties, including anti-inflammatory, antioxidant, immunomodulatory, anticancer, antidiabetic, antimicrobial, antiulcer, and neuroprotective properties. It is believed that Ayurveda possesses anti-inflammatory, antimicrobial, antiviral, antifungal, and anticancer properties. It is also believed to affect glucose metabolism and be beneficial for diabetes management positively. Several studies have demonstrated that *O. sanctum* has antidiabetic properties. Ezeani *et al*. (2017) demonstrated that an aqueous extract of *O. sanctum* leaves significantly decreased diabetic rodents' fasting blood glucose levels. In addition, *O. sanctum* has been shown to have a protective effect on various organs, including the pancreas, liver, and kidneys, which can be advantageous for preventing and managing complications associated with diabetes (Cohen, 2014). In conclusion, *O. sanctum* has traditionally been utilized for its medicinal properties and has demonstrated promising results in managing diabetes and its related complications. However, further research is needed to fully understand its mechanisms of action and potential therapeutic applications.

The present investigation, screened phytochemicals with antidiabetic properties from *O. sanctum*. Aiming for this objective, a pair of therapeutic molecular focal points, as illustrated in Figure 1; namely, sodium-glucose cotransporter type 2 inhibitors (SGLT2) and peroxisome proliferator-activated receptor-gamma (PPAR-γ), both of which have been documented in previous studies for their efficacy against T2D, were chosen. Focusing on these targets is their ability to address insulin resistance and glucose control.

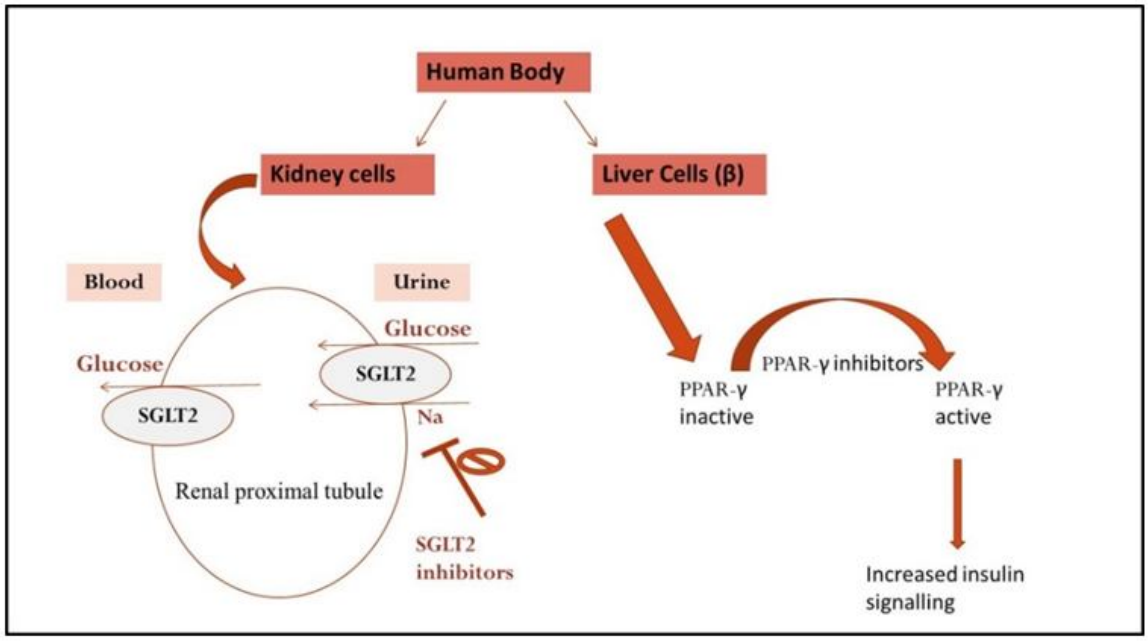


Figure 1: Mechanism of action of SGLT2 inhibitors and PPAR-γ agonist.

The sodium-glucose cotransporter 2 (SGLT2) protein is pivotal in handling glucose reabsorption within the kidney. By impeding the function of SGLT2, there is a consequential rise in the excretion of glucose through urine, resulting in a decline in blood glucose levels. A fresh category of medications known as SGLT2 inhibitors, which are relatively recent in development, are harnessed for managing type 2 diabetes (T2D). Scientific investigations have conclusively exhibited that SGLT2 inhibitors effectively curtail blood glucose concentrations, augment sensitivity to insulin, and diminish the susceptibility to cardiovascular ailments among individuals afflicted with T2D.

For example, in individuals with T2D who are at an elevated risk of experiencing cardiovascular complications, the SGLT2 inhibitor empagliflozin has demonstrated a notable capacity to decrease the likelihood of cardiovascular fatality markedly, incidents of nonfatal heart attack and instances of nonfatal stroke. Canagliflozin, an SGLT2 inhibitor, has been shown to reduce the risk of cardiovascular events in T2D patients with preexisting cardiovascular disease, as reported by Wanner *et al*. (2016). As a result, SGLT2 inhibitors are seen as a potentially helpful treatment for T2D and associated consequences.

SGLT2 inhibitors lower the renal threshold for glucose excretion because these drugs limit glucose reabsorption in the proximal convoluted tubule. Chronic hyperglycemia in type 2 diabetes patients is improved by increased renal glucose excretion. SGLT2 inhibitors pose little danger of hypoglycemia because their mechanism of action is unrelated to insulin, and they do not overstimulate or exhaust beta cells.

PPAR-γ (peroxisome proliferator-activated receptor gamma) is a nuclear receptor essential for glucose homeostasis and insulin sensitivity. Its activation enhances glucose metabolism by increasing insulin sensitivity and decreasing insulin resistance. Consequently, PPAR-γ agonists are therapeutic targets for treating T2D (Qin *et al*., 2023). Multiple studies have found an association between PPAR-γ and diabetes and its complications (Hye Khan *et al*., 2018). PPAR-γ agonists could protect against diabetic retinopathy by

lowering oxidative stress and inflammation (Behl *et al*., 2016). PPAR-γ is still being studied for its potential as a therapeutic target in treating diabetes and its consequences.

Using AutoDock tools, we performed a molecular docking analysis of 35 phytochemicals from *O. sanctum* against PPAR-γ and SGLT2 targets. In order to identify prospective candidates for the treatment of T2D, we predicted their drug-like properties and toxicity levels. These findings may serve as a starting point for further optimization and synthesis of these phytochemicals into more effective and efficient therapeutics for diabetes management and treatment.

2. Materials and Methods

2.1 Construction of the phytochemical library

O. sanctum (Figure 2) is a herbaceous plant with potential therapeutic properties used for centuries in traditional medicine. Anti-inflammatory, antioxidant, and antimicrobial properties are well-known. In recent years, there has been a growing fascination with the potential role of this plant in diabetes management. Several studies suggested that *O. sanctum* may have antidiabetic properties. An investigation was conducted to analyze how this plant impacts the blood glucose levels of rodents with diabetes. *O. sanctum* extracts substantially decreased blood glucose levels and enhanced glucose tolerance in diabetic rats, according to a study (Ezeani *et al*., 2017). However, it is unknown which compounds possess anti-diabetic properties. A compilation of phytochemicals in sdf and mol2 formats was generated through a comprehensive search of scientific literature, PubChem, and ZINC databases. The intention was to identify potential candidates with antidiabetic properties from *O. sanctum*.

Figure 2: *Ocimum sanctum* L. plant.

2.2 Preparation of protein targets against T2D

In order to identify potential new antidiabetic candidates, we conducted a thorough search for molecular targets of T2D using various online databases, including the potential drug target database, DrugBank, PharmGkb, and therapeutic targets Database. Our search yielded multiple molecular targets that have been associated with T2D. We procured these targets' corresponding X-ray crystallographic structures from the protein data bank maintained by the Research Collaboratory for Structural Bioinformatics. These structures served as the receptors in our subsequent molecular docking experiments.

2.3 Preparation of ligands

We obtained the 3D structures of all phytochemicals present in *O. sanctum* in both sdf and mol2 formats from PubChem. We converted these structures into pdb format using the OpenBableGUI software to make them compatible for further analysis. For our molecular docking experiments, we used N-[2-(dimethylamino)ethyl]-2-methyl-2-[4-[4-[[2-methyl-5-[(2S,3R,4R,5S,6R)-6-methylsulfanyl-3,4,5-tris(oxidant)oxan-2-yl]phenyl]methyl]phenyl]butanoylamino]propanamide as a reference ligand of SGLT2 and 5-({4-[(6-methoxy-1-methyl-1H-benzimidazol-2-yl)methoxy]phenyl}methyl)-1,3-thiazolidine-2,4-dione (7VA) as a reference molecule of PPAR-γ. These reference ligands were already attached to their respective protein structures, which were downloaded from PDB, and were used to determine the active site of the proteins and for our subsequent molecular docking experiments.

2.4 Virtual screening by molecular docking

This research employed Swiss PDB Viewer and CastP server to ascertain the active binding sites of molecular targets. Default settings were maintained for other parameters. To conduct virtual screening, AutoDock software within Python molecular viewer (Version 1.5.6) was utilized for molecular docking. Conformations with the most favourable binding energy (measured in kcal/mol) were cherry-picked for subsequent analysis. The intricate protein-ligand 2D interactions, comprising hydrogen bonds and bond lengths, underwent scrutiny *via* Ligplot + v.1.4.5 software and PyMOL software.

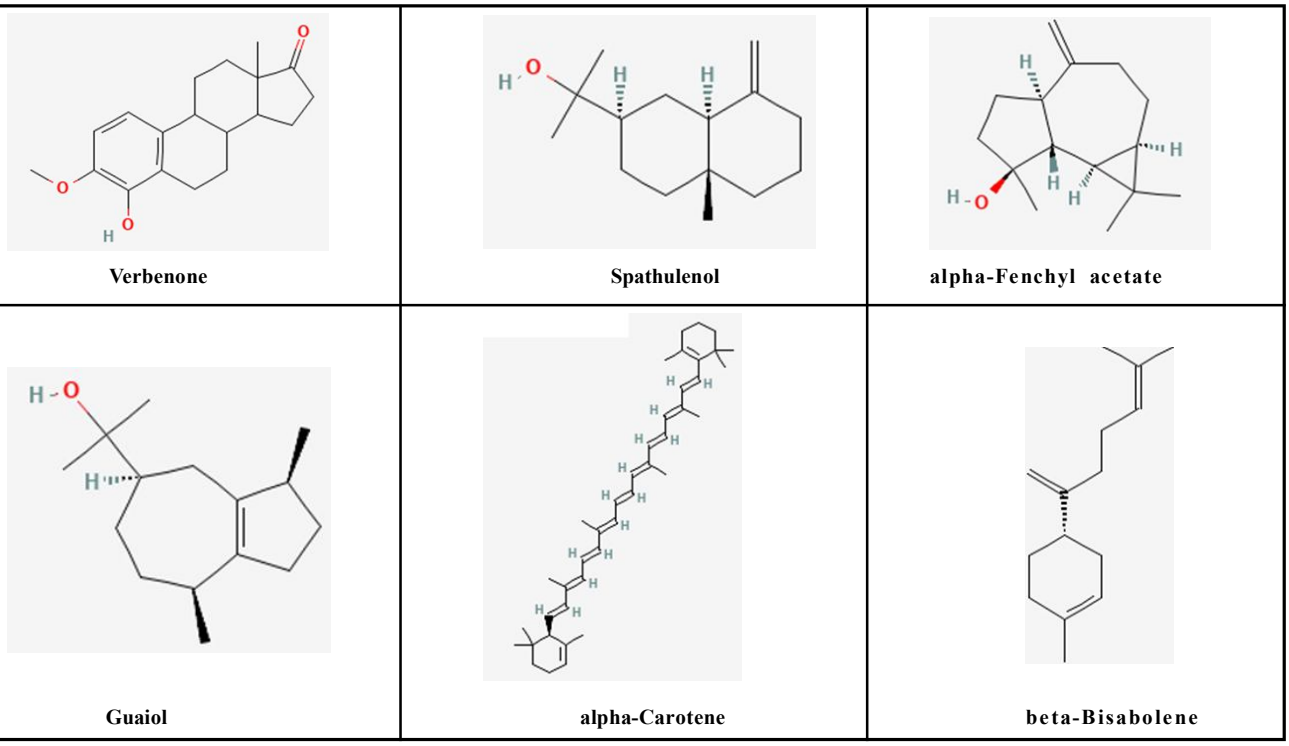
2.5 Drug likeness prediction

The potential of screened phytochemicals to serve as drug candidates were assessed through QSAR investigations conducted on the molinspiration server (Rosell and Crino, 2002). Using DruLiTo, calculations were performed for Lipinski's rule of five, Veber filter, Ghose filter, Muegge rule, and Egan rule to determine drug-likeness.

Table 1: Phytochemical library of *O. sanctum*

S.No.	Name of phytochemicals	Compound CID
1	Eucalyptol	CID2758
2	Eugenol	CID3314
3	linalool	CID6549
4	Acetyleugenol	CID7136
5	alpha-Phellandrene	CID7460
6	gamma-Terpinene	CID7461
7	Estragole	CID8815
8	6-Methyl-5-hepten-2-one	CID9862
9	Carvacrol	CID10364
10	Myrtenol	CID10582
11	Terpinolene	CID11463
12	3-Octanol	CID11527
13	Fenchone	CID14525
14	Sabinene	CID18818
15	1-Octen-3-OL	CID18827
16	Verbenone	CID22284
17	Myrcene	CID29025
18	4-Allylphenol	CID31253
19	beta-Eudesmol	CID68148
20	Spathulenol	CID91457
21	alpha-Fenchyl acetate	CID92231
22	β-sitosterol	CID107217
23	Guaiol	CID227829
24	(Z)-beta-Ocimene	CID532050
25	cis-3-Hexen-1-ol	CID5281167
26	Cinnamyl acetate	CID5282110
27	(Z)-alpha-Bisabolene	CID5352653
28	Damascenone	CID5366074
29	alpha-Carotene	CID6419725
30	d-Borneol	CID6252009
31	beta-Bisabolene	CID10104370
32	(-)-alpha-Cadinol	CID10398656
33	alpha-Selinene	CID10856614
34	(-)-Globulol	CID12304985
35	Zizanene	CID12306046

Verber rule indicates that drug-like molecules should possess a Rotatable Bond Count of d ≤ 10 and TPSA d ≤ 140. The Ghose filter, on the other hand, evaluates drug-likeness using logP values (– 0.4 to 5.6), Molar refractivity (40-130), M.W. (160-480), atom count (20-70), and TPSA d ≤ 140. Following Lipinski's rule, drug-like molecules should exhibit a Log *p* value of d ≤ 5, M.W. d ≤ 500, HBA count d ≤ 10, and HBD count d ≤ 5. The Egan rule recommends that compounds with a TPSA value of less than 140 Å² are more likely to have good bioavailability. The Muegge rule, also known as the rule of three, suggests that compounds with a molecular weight (M.W.) of less than 300, cLogP value of less than 3, and less than three hydrogen bond donors and acceptors are more likely to be drug-like and have good oral bioavailability. These rules were used to select potential ligands.



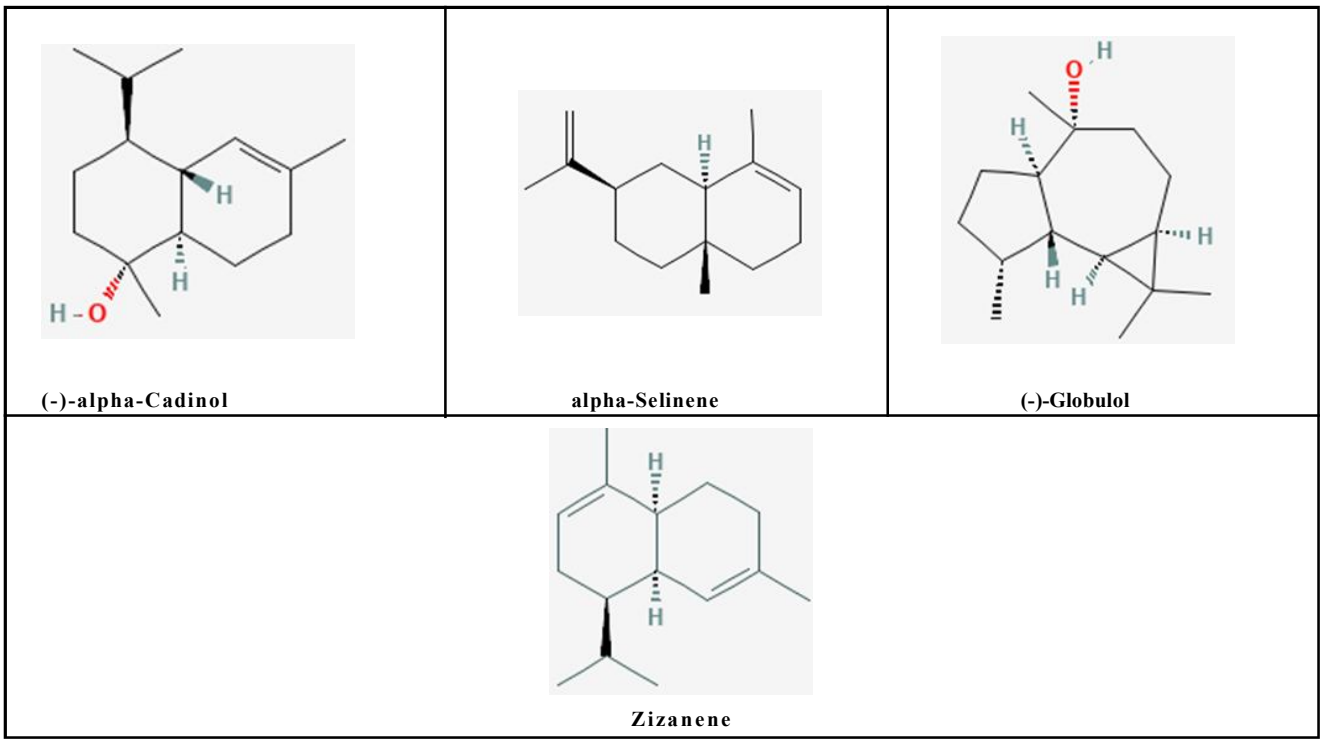


Figure 3: 2D structure of selected phytochemicals of *Ocimum sanctum* L.

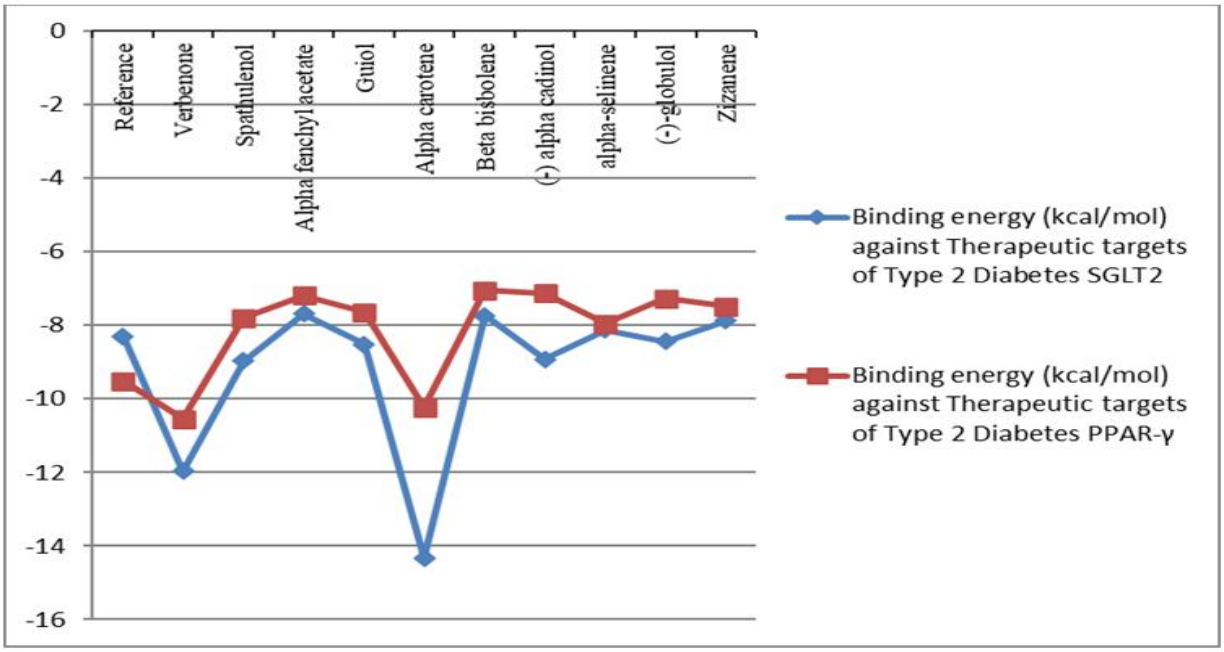


Figure 4: The visual depiction illustrates the binding energy of various phytochemicals found in *Ocimum sanctum L.* concerning therapeutic targets associated with T2D.

(References: PPAR-γ :- Rivoglitazone; SGLT2 :- LX2761)

2.6 Analysis of absorption, distribution, metabolism, excretion, and toxicity (ADMET)

ADMET encompasses the pharmacokinetic attributes of ligands about their absorption, distribution, metabolism, excretion, and impact on the human body's well-being. To evaluate the toxicity patterns exhibited by the identified phytochemicals, we used the admetSAR prognostic utility (http://lmmd.ecust.edu.cn:8000). This tool facilitated the prediction of diverse parameters, including eye

irritation (E.I.), absorption within the human intestines (HIA), traversal of the blood-brain barrier (BBB), permeability through Caco-2 cell layers, and the likelihood of acute toxicity as indicated by the LD_{50} value.

3. Results

3.1 Construction of the phytochemical library

In order to make an entire phytochemical library for *O. sanctum*, 35 compounds from research papers and the PubChem database were gathered. PubChem was used to get the 3D structures of each phytochemical, and the complete list of *O. sanctum* phytochemicals is shown in Table 2 below.

3.2 Protein targets

Utilizing the Protein Data Bank (http://www.rcsb.org), we accessed 3D crystal structures of various molecular targets such as SGLT2 (PDB ID: 7wmv) and PPAR-γ (PDB ID: 5u5l), which were then employed in the research. Before the docking process, all aqueous and fluid molecules in the PDB file were manually eliminated due to their insignificance in the protein's functionality. Autodock Tools added polar hydrogen atoms and standardized nonpolar hydrogen atoms while the protein receptor was transformed from the PDB format to the PDBQT format. All other preparatory decisions concerning the receptor were retained in their original state.

Table 2: Binding energy of various *Ocimum sanctum* L. phytochemicals against T2D therapeutic targets

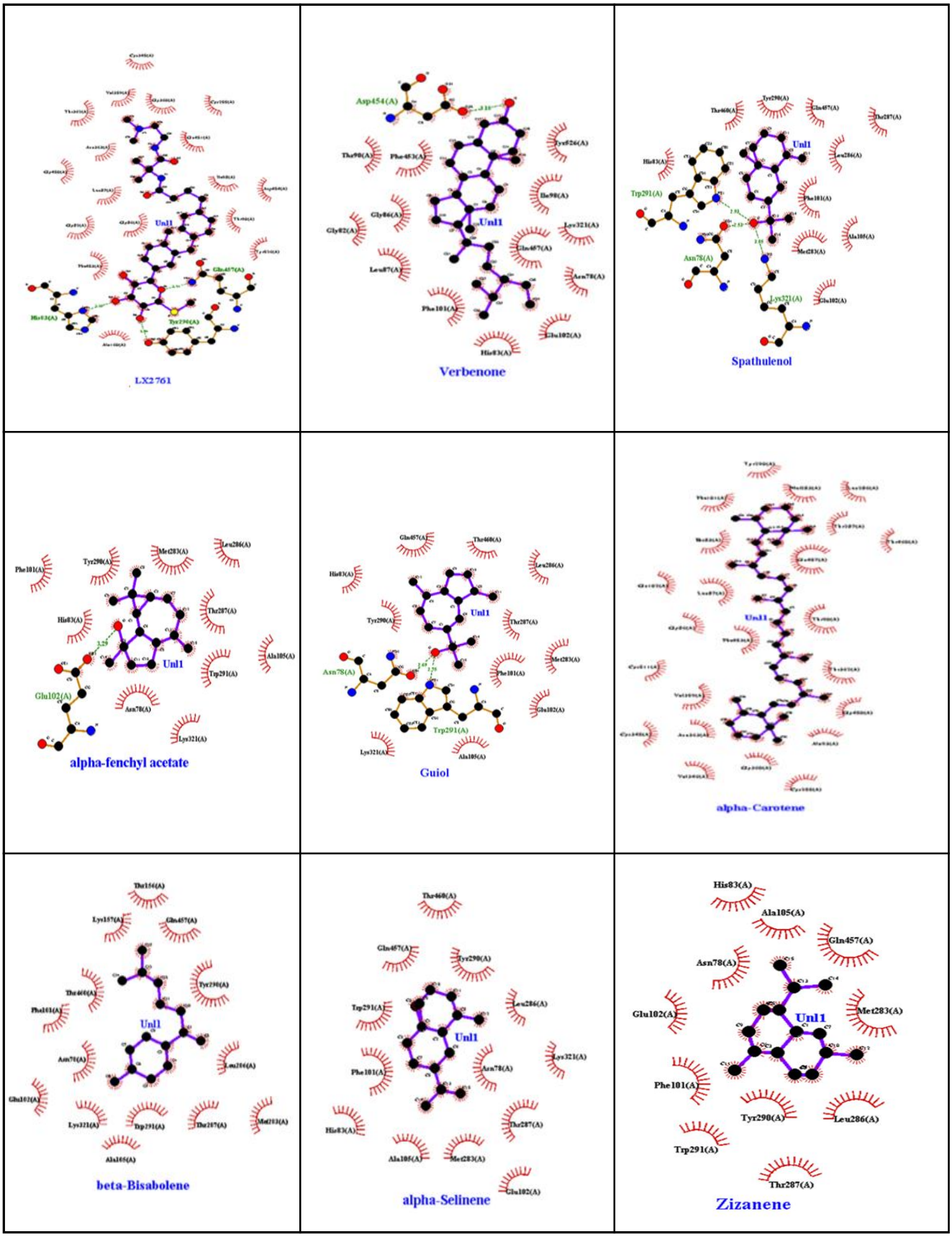
S.No.	Potent phytochemical of *O. sanctum*	Binding energy (kcal/mol) against therapeutic targets of T2D	
		SGLT2	PPAR-γ
1	Rivoglitazone	—	– 9.51
	LX2761	– 8.29	—
2	Verbenone	– 11.97	– 10.54
3	Spathulenol	– 8.97	– 7.8
4	alpha fenchyl acetate	– 7.69	– 7.19
5	Guiol	– 8.52	– 7.64
6	alpha carotene	– 14.33	– 10.24
7	beta bisbolene	– 7.73	– 7.04
8	(-) alpha cadinol	– 8.92	– 7.13
9	alpha selinene	– 8.12	– 7.95
10	(-)-globulol	– 8.44	– 7.26
11	Zizanene	– 7.87	– 7.48

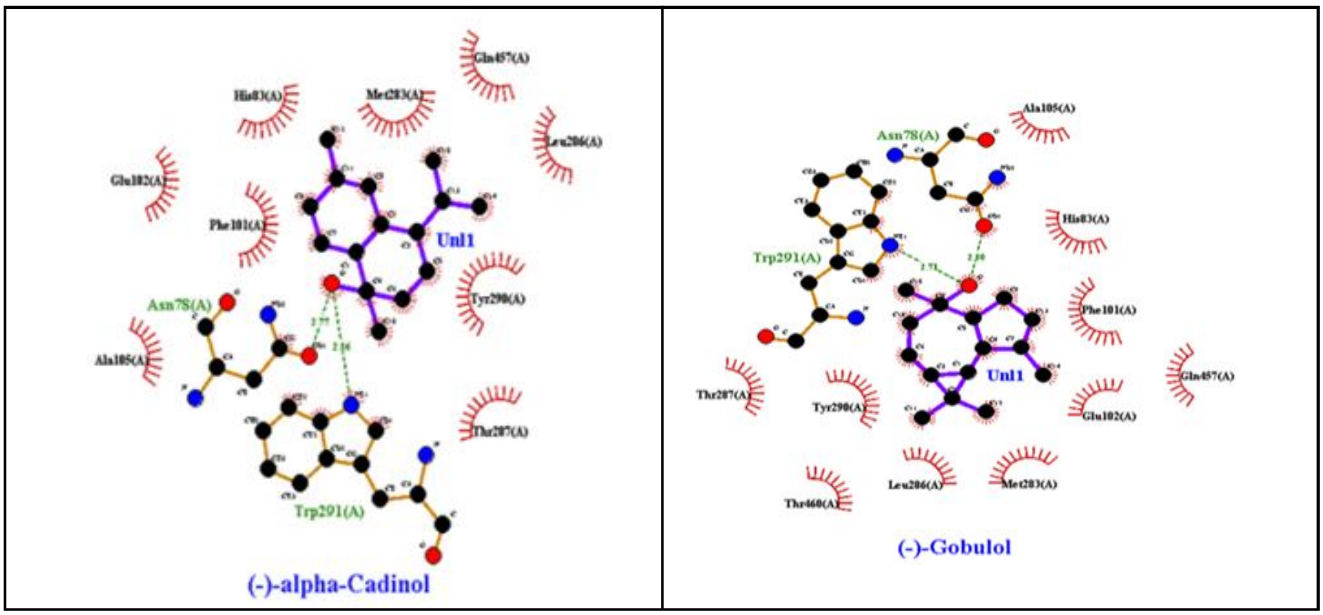
3.3 Molecular docking analysis

The results of molecular docking for two molecular targets, SGLT2 and PPAR-γ, revealed that ten of the thirty-five screened phytochemicals demonstrated an excellent binding affinity and superior binding modes compared to the reference molecules (LX2761 and Rivoglitazone). The 2D structures of the screened phytochemicals are depicted in Figure 3. The binding energies of the two molecular targets with eleven phytochemicals are illustrated in the line chart in Figure 4. Verbenone, spathulenol, alpha fenchyl acetate, guiol, alpha-carotene, beta bisabolene, (-) alpha cadinol, alpha-selinene, (-)-globulol, and zizanene exhibited variable binding affinity with each target, with fluctuations observed in the range of –10.54 to –11.97 kcal/mol. The best binding energy for SGLT2 was alpha-carotene (–14.33 kcal/mol), while the best binding energy for PPAR-γ was found with verbenone (–10.54 kcal/mol). The binding energy range for these phytochemicals with SGLT2 and PPAR-γ was from –14.33 to –7.69 kcal/mol and from –10.54 to -7.04 kcal/mol, respectively (Table 2). In SGLT2, the binding energy of six phytochemicals was superior to the reference, with slightly lower binding energy observed for alpha fenchyl acetate (–7.69 kcal/mol) and beta bisbolene (–7.73 kcal/mol). However, for PPAR-γ, two phytochemicals (verbenone and alpha-carotene) demonstrated less binding energy than the reference molecules.

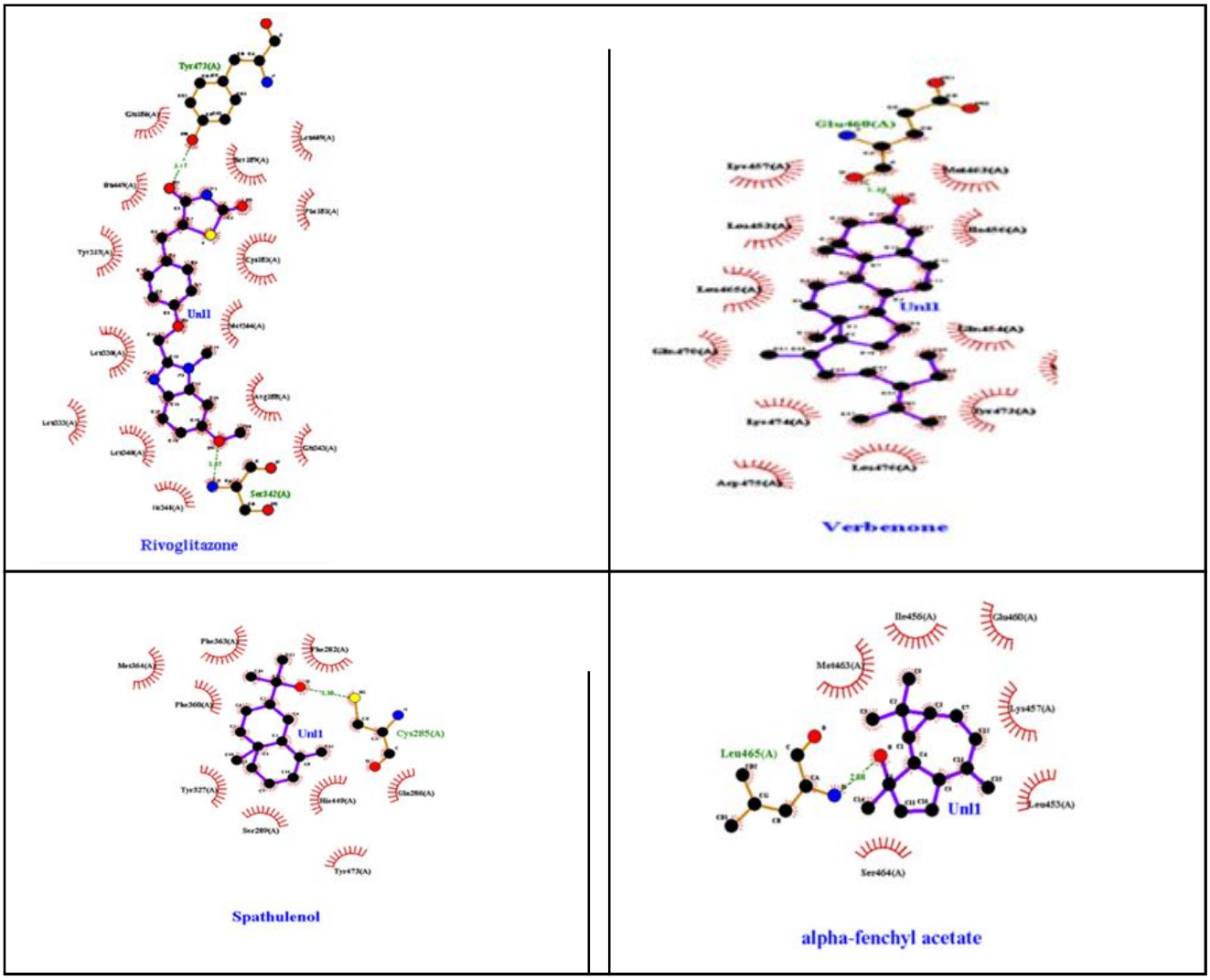
3.4 Visualization of ligand-receptor in the reactions using the Ligplot program in 2D

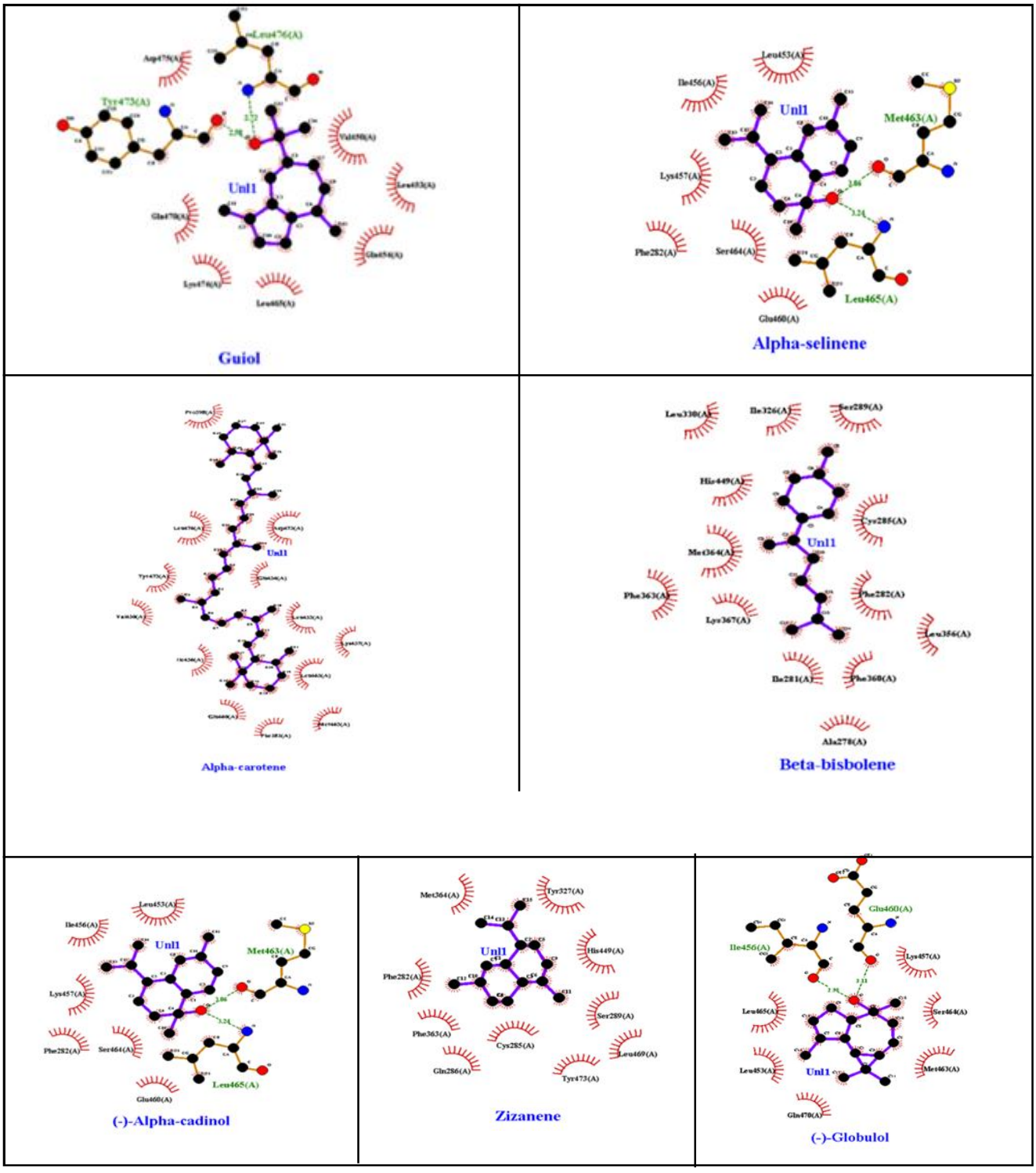
Figure 5 shows the 2D interactions between the different phytochemicals that were tested and the two molecular targets of interest, as well as their hydrogen bonding (HB) interactions with the reference molecules and their hydrophobic interactions (HI) with different amino acid residues (one letter code) (Tables 3 a, b). The green lines with dots show the constrained hydrogen bonds, while the red arcs with sparks show the residues that make hydrophobic contacts with the phytochemicals. The red rings and ellipses show protein residues in the same place in three dimensions. Based on molecular docking and ligplot interaction results, eleven of the sixty molecules could be used to treat diabetes. These compounds include verbenone, spathulenol, alpha fenchyl acetate, guiol, alpha-carotene, beta-bisabolene, (-) alpha cadinol, alpha-selinene, (-)-globulol, and zizanene.


LX2761
Verbenone
Spathulenol
alpha-fenchyl acetate
Guiol
alpha-Carotene
beta-Bisabolene
alpha-Selinene
Zizanene



(a) 2D interaction of hit phytochemicals against SGLT2





(b) 2D interaction of hit phytochemicals against PPAR-γ

Figure 5: Displays the 2D interactions between the screened phytochemicals and the binding sites of SGLT-2 and PPAR-γ in 2D using the Ligplot program. Red eye-lashes symbolized the hydrophobic interactions between the ligands and binding site residues, while a green line indicated the length of hydrogen bonds. Ligand structures took the form of robust purple sticks, contrasting with the brown sticks representing binding site residues. Further clarification on colour references is available in the online version of this article's figure legend.

Table 3 (a, b): Amino acids involved in Interactions between phytochemicals and binding sites

S.No.	Phytochemical (SGLT2)	Interaction type	
		HB	HI
1	LX2761	H, Y, G	T, F, G
2	Verbenone	D	F, G, Q
3	Spathulenol	W, N, K	M, F, L
4	alpha fenchyl acetate	E	H, T, W
5	Guiol	N, W	Y, T, A
6	alpha carotene	666	V, L, T
7	beta bisbolene	666	W, Y, Q
8	(-) alpha cadinol	N, W	F, Y, M
9	alpha selinene	666	N, W, F
10	(-)-globulol	N, W	L, E, F
11	Zizanene	666	M, Y, L

S.No.	Phytochemical (PPAR-γ)	Interaction type	
		HB	HI
1	Rivoglitazone	Y, S	Q, C, M
2	Verbenone	E	M, I, K
3	Spathulenol	C	F, H, S
4	alpha fenchyl acetate	L	K, L, M
5	Guiol	Y	E, V, D
6	alpha carotene	666	I, Y, L
7	beta bisbolene	666	F, M, C
8	(-) alpha cadinol	L, M	S, G, K
9	alpha Selinene	L, M	S, G, K
10	(-)-globulol	E, I	K, L, S
11	Zizanene	666	Y, H, C

Table 4 (a, b): Molecular characteristics of the analyzed phytochemicals determined using the molinspiration tool, SwissADME, and DruLiTo

S.No.	Molecule	Molecular weight	Polar surface area	Lipophilicity		LogS(ESOL)	log Kp (cm/s)
				iLOGP	MLOGP		
1	Verbenone	300.39	46.53	2.87	3.06	-3.79	-5.93
2	Spathulenol	222.37	20.23	3.06	3.67	-3.51	-5
3	alpha fenchyl acetate	220.35	20.23	3.04	3.67	-3.17	-5.44
4	Guiol	222.37	20.23	3.08	3.67	-3.09	-5.48
5	alpha carotene	536.87	0	3.08	3.67	-3.09	-5.48
6	beta bisbolene	204.35	0	3.67	4.53	-4.89	-2.98
7	(-) alpha cadinol	222.37	20.23	3.15	3.67	-3.26	-5.29
8	alpha-selinene	204.35	0	3.31	4.63	-4.32	-3.85
9	(-)-globulol	222.37	20.23	3.01	3.81	-3.57	-5
10	Zizanene	204.35	0	3.36	4.63	-3.61	-4.65
	Drug likeliness						

S.No.	Molecule	Lipinski rule	Ghose filter	Veber filter	Egan rule	Muegge rule	Bioavailability score
1	Verbenone	0	0	0	0	0	0.55
2	Spathulenol	0	0	0	0	1	0.55
3	alpha fenchyl acetate	0	0	0	0	1	0.55
4	Guiol	0	0	0	0	1	0.55
5	alpha carotene	0	0	0	0	1	0.55
6	beta bisbolene	1	0	0	0	2	0.55
7	(-) alpha cadinol	0	0	0	0	1	0.55
8	alpha-selinene	1	0	0	0	2	0.55
9	(-)-globulol	0	0	0	0	1	0.55
10	Zizanene	1	0	0	0	1	0.55

3.5 Prediction of drug-likeness

Drug-likeness filters can aid in early preclinical development, preventing costly failures in later stages of preclinical and clinical trials. This study observed that phytochemicals with high logP values did not exhibit good docking scores with any receptor, while those with intermediate logP values demonstrated favourable docking scores. Phytochemicals with an intermediate H-bond acceptor and logP value were deemed potential antidiabetic agents. Conversely, phytochemicals with high H-bond acceptor values did not exhibit desirable activity. Interestingly, there was no correlation observed between logP and docking scores. Table 4 (a, b) summarises the logP values and drug-likeness properties of various phytochemicals evaluated based on Lipinski's rule of 5, Ghose filter, verber filter, Egan rule, and Muegge rule. Most hit compounds, including verbenone, spathulenol, alpha fenchyl acetate, guiol, alpha carptene, alpha cadinol, and (-) globulol, adhered to Lipinski's rule of five. All ten selected phytochemicals followed Ghose rule, Veber filter, and Egan rule, while only one phytochemical, verbenone, followed Muegge rule.

Table 5: ADMET characteristics of screened compounds derived from admetSAR

S.No.	Phytochemicals	AdmetSAR results					
		Eye irritation	Human intestinal absorption	LD50 (mol/kg)	Blood-brain barrier	Caco2 permeability	Carcinogen
1	Verbenone	EI-	HIA+	1.24	BBB+	Ca c02+	Non-oncogenic
2	Spathulenol	EI+	HIA+	1.77	BBB+	Ca c02+	Non-oncogenic
3	alpha fenchyl acetate	EI-	HIA+	2.12	BBB+	Ca c02+	Non-oncogenic
4	Guiol	EI+	HIA+	0.85	BBB+	Ca c02+	Non-oncogenic
5	alpha carotene	EI-	HIA+	1.49	BBB+	Ca c02-	Non-oncogenic
6	beta bisbolene	EI+	HIA+	1.89	BBB+	Ca c02+	Non-oncogenic
7	(-) alpha cadinol	EI-	HIA+	0.86	BBB+	Ca c02+	Non-oncogenic
8	alpha selinene	EI+	HIA+	2.01	BBB+	Ca c02+	Non-oncogenic
9	(-)-globulol	EI+	HIA+	2.66	BBB+	Ca c02+	Non-oncogenic
10	Zizanene	EI+	HIA+	1.81	BBB+	Ca c02+	Non-oncogenic
11	Control drug (bexagliflozin)	EI-	HIA+	2.41	BBB+	Ca c02-	Non-oncogenic
12	Control drug (ertugliflozin)	EI-	HIA+	1.80	BBB+	Ca c02-	Non-oncogenic

3.6 ADMET

By considering factors like Absorption, Distribution, Metabolism, and Excretion (Cheng *et al*., 2012), the admetSAR server can analyze the pharmacokinetic characteristics of compounds. Table 3 shows the results of the admetSAR study. The AdmetSAR analysis provided predictions for human intestinal absorption (HIA + or HIA-), Caco-2 permeability (permeable or not permeable), blood-brain barrier penetration (BBB + or BBB-), eye irritation (E.I.), and carcinogens (oncogenic or not oncogenic). The phytochemicals had a good range of ADMET profiles, which shows how well they could work as robust drug options. Log S measures how well the ligands mix with water, which should be between -6.5 and 0.5. The LD_{50} for acute toxicity to rats was between 0.85 and 2.66 mol/kg. Table 5 shows that the result was the same as with the control drug. So, these phytochemicals meet all the listed requirements, and we can say that they could be used to make a better drug for people with diabetes.

4. Discussion

T2D is a long-term metabolic problem marked by high blood sugar and resistance to insulin. T2D is becoming more common worldwide and is seen as a significant public health risk. Various medicinal plants have been reported to have hypoglycemic effects and may be used as an adjunct to conventional treatment of T2D. These plants may lower blood sugar in different ways, such as by making more insulin, making insulin work better, and stopping carbs from being broken down and absorbed (Neelakantan *et al*., 2014); several herbal mixtures with *O. sanctum*, also called "holy basil," have been shown to lower blood sugar and improve oral glucose tolerance in both normal rats and rats that have been given alloxan to make them diabetic. A research study investigated how a blend of holy basil and various medicinal herbs influenced blood sugar levels in normal rats and rats with diabetes induced by alloxan (Gupta *et al*., 2002). Another study investigated the hypoglycemic effects of holy basil and other medicinal herbs on insulin sensitivity, lipid profile, and antioxidant status in alloxan-induced diabetic rats (Khan *et al*., 2012). The primary focus of the current research was to explore the critical phytochemicals found in *O. sanctum* to discover more affordable, safer, and more effective drugs for T2D treatment. The current investigation delved into the intricate molecular mechanisms underlying the inhibitory action of the phytochemicals in *O. sanctum* against the therapeutic targets of T2D, specifically SGLT2 and PPAR-γ. This was accomplished through the utilization of molecular docking techniques. These are alpha-carotene (B.E -14.33, -10.24), verbenone (B.E.-11.97, B.E10.54), spathulenol (B.E. 8.97, -7.80), -(-) globulol (B.E. 8.44, -7.26), alpha-selinene (B.E.-8.12, B.E7.95) with binding energy SGLT2 and PPAR-γ, respectively, measured in kcal/mol. The findings of this study provide compelling evidence that certain phytochemicals found in *O. sanctum*, including alpha-Carotene, verbenone, spathulenol, (-)-globulol, and alpha-selinene, may be promising candidates for treating diabetes by targeting PPAR-γ, and SGLT2.

Every screened phytochemical follows the drug-likeness rule, fulfilling the requirements for LogS and lethal factor concentration (LD_{50}). Furthermore, the results of molecular docking simulations revealed that all of these phytochemicals exhibit binding solid energies with the two receptors associated with T2D, along with favourable hydrogen bond lengths between amino acids and ligands. These observations suggest that these phytochemicals could be potent ligands for their targets. Upon comparing with reference compounds, it was discovered that five of the ten screened phytochemicals possess potential as antidiabetic drug candidates. Some phytochemicals have been investigated for their potential therapeutic effects against various diseases, including diabetes. Alpha-carotene may be beneficial in cancer; it suggested that higher levels of alpha-carotene in the blood may be related to a lower risk of developing certain types of cancer (Park *et al*., 2007). Another study reported that alpha-carotene might have the potential as a therapeutic agent for treating T2D due to its antioxidant and anti-inflammatory effects (Bhatt and Patel, 2014). Spathulenol has anti-inflammatory and analgesic effects in animal models; initial findings indicate that this could be explored as a treatment for pain and inflammation (Chou *et al*., 2018). Due to its ability to increase insulin secretion and improve glucose uptake in cells, verbenone may have the potential as a hypoglycemic agent (Tijjani *et al*., 2022). Some potential strengths of this article are a novel approach, reduced resource requirements, and drug-likeness prediction; limitations are a lack of experimental validation and potential false positives/negatives.

5. Conclusion

This study investigated the potential antidiabetic activity of *O. sanctum* compounds via molecular interaction with T2D therapeutic targets. Alpha-carotene, verbenone, spathulenol, (-)-globulol, and alpha-selinene were identified as potential hits based on their high binding affinity, drug-likeness, and ADMET prediction. The higher selectivity scores of these compounds concerning all T2D therapeutic targets indicate their potential as antidiabetic agents. These findings provide credence to the traditional application of *O. sanctum* in managing diabetes and imply that these compounds could be studied in vitro and *in vivo* to find innovative possibilities for developing antidiabetic medicines. These findings provide valuable insights for researchers seeking to develop effective formulations for managing T2D.

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Conflict of interest

The authors declare no conflict of interest relevant to this article.

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