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Original Article

# *In silico* Decoding of the Antidiabetic Potential of *Sphaeranthus indicus* Linn.: A Network Pharmacology and Molecular Docking Integration

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**ABSTRACT**

Diabetes mellitus is a chronic disease that leads to persistent high blood sugar along with dysfunction of various metabolic systems. Though effective, the latest drug therapies still have some problems like causing side effects and not being able to stop the progression of the loss of cell mass. To study the anti-diabetic potential of *Sphaeranthus indicus* Linn., a plant that is highly valued in Ayurvedic medicine, this research employs a computational framework linking network pharmacology, molecular docking, and ADME analysis. Screening showed 57 phytochemicals of which 14 significantly interacted with 123 genes associated with Type 2 Diabetes. Through network analysis, the central hub genes ACE, GSK3B, PTGS2, and PTPN1 were identified. 1-triacontanol and beta-sitosterol, two compounds from molecular docking, were found to have strong binding affinity to the major targets PPARgamma, GSK3beta, and ACE with the former having a comparable or even better affinity than the reference drug rosiglitazone. Besides, they exhibited high binding potential for EphA4, which might unveil a pathway for the control of hyperglucagonemia. ADME analysis showed these lead compounds to be drug-like candidates but with a caveat of somewhat limited solubility. These results justify the use of *S. indicus* as an effective multi, target medicine for not only diabetes but also its vascular complications at the molecular level.

**Keywords:** Ayurveda, Diabetes Mellitus, *In silico*, Reverse Pharmacology, *Sphaeranthus indicus*.

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## INTRODUCTION

One of the most significant public health issues of the twenty-first century is diabetes mellitus (McGee and Johnson, 2013). It is a complicated, multi-systemic metabolic illness marked by persistent hyperglycemia brought on by deficiencies in insulin secretion, action, or both (Ewing and Parvez, 2010). According to estimates from the International Diabetes Federation (IDF), hundreds of millions of individuals worldwide suffer from diabetes; this figure is expected to climb sharply in the upcoming decades as a result of urbanization, aging populations, and the rising rates of obesity and sedentary lifestyles (Saeedi *et al*., 2019).

Type 2 Diabetes Mellitus (T2DM) or Non-Insulin Dependent Diabetes Mellitus (NIDDM) comprises the major part of diabetes and related disorders. Other types include Insulin Dependent Diabetes Mellitus (IDDM), also called Type 1 diabetes, gestational onset diabetes mellitus, etc. (Solis-Herrera, 2018). The disease mechanism basically involves two main pathologies: insulin resistance of peripheral tissues (muscle, liver, and adipose tissue) and pancreatic β-cell failure (Zhao *et al*., 2023).

At the very beginning, tissues do not respond effectively to insulin. The liver, despite being supplied with insulin, goes on producing glucose (unrestrained gluconeogenesis), and skeletal muscle is also unable to take up glucose efficiently (Onyango, 2022). Cells of the pancreas secrete more insulin to compensate for the hyperglycemia (hyperinsulinemia). Finally, cells become exhausted and are incapable of maintaining the compensatory production of insulin. Cell failure, with its associated decline in insulin secretion, is the critical event in the progression to overt diabetes. Nevertheless, the major culprits are the deleterious effects of glucotoxicity, lipotoxicity (abnormally high levels of fatty acids and lipid metabolites), oxidative stress, and low-grade inflammation on cells. Recent research attributes T2DM not only to β-cells but also to α-cells. Glucagon secretion is inhibited by insulin in normal persons (Poitout *et al*., 2010). Meanwhile, in diabetes, this paracrine regulation is abolished resulting in glucagon secretion (hyperglucagonemia) which is a major factor in the drive of hepatic glucose production. Persistent high blood sugar level slowly damages blood vessels (Huising, 2020). The complications caused by small blood vessel damage include: nephropathy (which if untreated leads to kidney failure), retinopathy (which if untreated leads to blindness), and neuropathy (which if untreated can lead to amputation by

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damage to the nerves). The main cause of death among diabetics is macrovascular complications, like coronary artery disease and stroke (Iwasaki, 2025).

Various antidiabetic drugs are currently available, including biguanides (Metformin), sulfonylureas, Thiazolidinediones (TZDs), DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists (Khan, 2024). However, despite their effectiveness, these drugs are often accompanied by limitations. For example, Metformin is known to cause gastrointestinal discomfort; sulfonylureas may lead to hypoglycaemia and weight gain; and TZDs have been associated with fluid retention and an increased risk of heart failure (Susilawati, 2023). Additionally, very few drugs can halt the gradual loss of β-cell mass or simultaneously target the inflammatory and oxidative mechanisms that contribute to the disease. Therefore, the search for new therapeutic paradigms is very urgent, especially naturally derived ones which might combine multi-targeted efficacy with improved safety profiles.

Ethnopharmacology, the scientific study of indigenous medicinal practices, is an essential connection that helps to integrate traditional knowledge with modern medicine. Since the very beginning, plants have been the starting point of some of the most significant anti-diabetic medications. Apart from modern drugs, metformin, as the most commonly prescribed medication for T2DM, is known to come from a plant called *Galega officinalis* (French lilac) that contains guanidine (Bailey, 2017).

The Indian subcontinent, being the home of three ancient systems of medicine, Ayurveda, Siddha and Unani, is rich in medicinal plants. Ayurvedic literature refers to diabetes as Madhumeha and lists it as a Maharoga (major disease) (Balkrishna *et al*., 2025). The mode of treatment in Ayurveda is all-encompassing, with the use of Rasayana herbs for tissue rejuvenation and the restoration of metabolic balance (Agni). An example of such a plant, highly regarded but not yet thoroughly investigated at the molecular level in the context of diabetes, is *Sphaeranthus indicus* Linn.

*Sphaeranthus indicus* (fam. Asteraceae) is a fragrant, highly branched, annual herb that grows wild in India, Sri Lanka, Africa, and Australia. It is a typical plant of wet places and one of the weeds that come up in post-harvest rice fields. The plant can be easily recognized by the spherical globular heads of purple flowers and its toothed and winged stems (Singh, 2019). In Ayurveda, it is used in management of various disorders like such as glandular swellings, jaundice, urethral discharges, epilepsy (as a nervine tonic), urinary disorders and also diabetes. Some of these therapeutic applications are proved also by the folk wisdom of Bundelkhand, a region in the center of India, where people use the extract of the flower heads to control the blood glucose level and the paste made from the flowers is applied on the skin for reducing oedema and arthritis, an anti-inflammatory effect being added (Ramachandran, 2013).

Pharmacological evaluation has tested and confirmed these ethnomedical claims by showing that petroleum ether and alcoholic extracts of *S. indicus* performed significant hypoglycaemic effects in diabetic models induced by alloxan and streptozotocin by the reduction of blood glucose, the elevation of plasma insulin, the restoration of hepatic glycogen, the improvement of lipid profiles, and the attenuation of oxidative stress and inflammation. The bioactive compounds and the mechanisms whether insulin secretagogues, insulin sensitizers, or inhibitors of glucose absorption that go along with these effects are, however, not identified yet (Jadhav and Vaghela, 2024). Innovative drug discovery methods such as molecular docking, ADME prediction, and network pharmacology, are essential in the attempt to find the answer to this black box question. These *in silico* studies, when used together, provide a platform to examine the interactions at the atomic level, the pharmacokinetic liability, and the effects of the multi-target system, thus giving a logical, systems, based opening to unravel the molecular basis of the antidiabetic and metabolic effect of *S. indicus* (Gomes *et al*., 2024).

## METHODOLOGY

### Enlisting phytochemicals

List of phytochemicals present in the *Sphaeranthus indicus* was obtained from the databases including IMPPT (Vivek-Ananth, 2023) and KNAPSACK (Shinbo *et al*., 2006). Duplicates were removed and Canonical SMILES of the individual compounds were traced from the Pubchem database (Kim *et al*., 2016).

### Network construction

The sdf files of all phytochemicals were retrieved from PubChem (as and when required, their formats were converted using RDKit. Experimentally known targets for the compounds were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/), ChEMBL (https://www.ebi.ac.uk/chembl/), BioGRID (https://thebiogrid.org/) and BindingDB (bindingdb.org). For all the targets, associated diseases were retrieved from DisGeNET (https://disgenet.com/). Only those diseases that were associated with diabetes mellitus type 2 were retained, the remaining were filtered out. The list of compounds, their targets and diseases were input to Cytoscape (version 3.10.3) to generate a network. The network was manually assessed to retain only meaningful connections.

### Identification of the hub genes

Protein-protein interaction network was established using the STRING database (https://string-db.org/), The network was then again exported to cytoscape. CytoHubba (Chin *et al*., 2014) was used to find the HUB genes from the network. Hubba nodes were ranked by all the 10 methods available in the software, and the observations were then compared to find the most relevant targets for the docking.

## Molecular docking studies

ParDOCK+ (https://scfbio-iitd.res.in/pardock+/) was used for rigid protein/ligand docking of the chosen phytochemicals into the active site of the target protein. The docking tool works on the principle of Monte Carlo-based conformational search to find the best binding conformation of each ligand in a defined cavity. Binding affinities were calculated using the ParDOCK scoring function, which calculates the binding free energy (ΔG, kcal/mol) by cumulating the contributions from van der Waals interactions, electrostatic interactions, and desolvation terms. A good correlation between predicted and experimental binding affinities was found, and the protocol's dependability has previously been demonstrated on a wide range of protein/ligand complexes. All potential phytochemicals were docked into the active site's center, which was defined by the reference ligand co-crystallized in the PDB structure. Each ligand's optimal binding conformation and estimated binding energy were included in the docking data.

## ADMET analysis

To assess the translational potential of the identified phytochemicals, *in silico* ADME and drug-likeness analysis was conducted using SwissADME (https://www.swissadme.ch/), a web-based tool developed by the Swiss Institute of Bioinformatics. Important physicochemical characteristics, including Molecular Weight (MW), fraction $Csp^3$ as a gauge of molecular saturation, and Topological Polar Surface Area (TPSA), were predicted using SwissADME. The consensus LogP (Po/w), which is derived from the average of five models-iLOGP, XLOGP3, WLOGP, MLOGP, and Silicos-IT-was used to predict lipophilicity. The ESOL, Ali, and Silicos-IT models were used to predict aqueous solubility. Other pharmacokinetic characteristics including Blood-Brain Barrier (BBB) permeability, Gastrointestinal (GI) absorption, and P-glycoprotein (P-gp) substrate propensity were also assessed. Drug-likeness analysis was carried out in accordance with the satisfaction filters including Ghose, Veber, Egan, Muegge, and Lipinski's Rule of Five. By calculating synthetic accessibility scores and identifying Pan-Assay Interference Substances (PAINS) alerts, medicinal chemistry was also examined.

# RESULTS

## Phytochemicals present in *Sphaeranthus indicus*

After curating the databases like IMPPAT and Knapsack, it has been observed that, there are 57 reported phytochemicals present in various parts of *S. indicus*. The phytochemicals can be broadly divided as per their classes as follows (Table 1):

## Network construction using Cytoscape

The constructed network showed that the amongst the 57 phytochemicals present in the *Sphaeranthus indicus*, 14 phytochemicals target a total of 123 genes related to the diabetes mellitus type 2. The constructed network is depicted in the figure below, where green nodes represent phytochemicals, pink represent target genes and yellow nodes represent the correlated disease conditions to the diabetes mellitus type 2 (Figure 1).

## Protein-protein interaction

The PPI network of the finalized target was constructed using the string database.

**Table 1: Classification of Identified Phytochemicals According to Chemical Class.**

| Phytochemical Class | Identified Compounds | Number of Compounds |
|---|---|---|
| Monoterpene hydrocarbons | α-Pinene; β-Pinene; Camphene; Limonene; Myrcene; α-Terpinene; α-Phellandrene; (E)-β-Ocimene; *p*-Cymene; 2,5-Dimethoxy-*p*-cymene | 10 |
| Oxygenated monoterpenes | Linalool; Geraniol; Nerol; Citral; Neral; Camphor; *d*-Borneol; 4-Carvomenthenol; Geranyl acetate; α-Ionone; β-Ionone | 11 |
| Sesquiterpene hydrocarbons | β-Caryophyllene; Humulene; β-Elemene; β-Cubebene; (+)-δ-Cadinene | 5 |
| Oxygenated sesquiterpenes | Guaiol; β-Eudesmol; 10-epi-γ-Eudesmol; α-Muurolol; Selin-11-en-4α-ol; Proximadiol; Isodihydroagarofuran; α-Agarofuran | 8 |
| Diterpenoids / oxygenated diterpenes | Arteannuic alcohol; Telekin; Tricyclo(6.3.1.$0^{2,5}$)dodecan-1-ol, 4,4,8-trimethyl- | 3 |
| Triterpenoids / phytosterols | β-Sitosterol; Stigmasterol | 2 |
| Phenylpropanoids | Eugenol; Estragole; 4-Methoxycinnamaldehyde | 3 |
| Phenolic / polycyclic aromatic compounds | 5,7-Dimethoxyphenanthrene-2,6-diol; (3R,3aR,5aR,9bS)-3a-hydroxy-3-(hydroxymethyl)-5a,9-dimethyl-hexahydro-3H-benzo[g][1]benzofuran-2-one | 2 |
| Aliphatic alcohols | cis-3-Hexen-1-ol; 2-Hexen-1-ol; 1-Triacontanol | 3 |
| Long-chain alkanes | Pentacosane; Hentriacontane | 2 |
| Terpenoid-derived organic acids | Ilicic acid; 2α-Hydroxycostic acid | 2 |
| Nitrogen-containing compounds | Ethyl *N*-phenylcarbamate; Pheanthine; Sphaerindicin | 3 |

The constructed network had 121 nodes, 797 edges and average node degree of 13.2.

The calculated average local clustering coefficient was 0.465. The expected number of edges was 239 and PPI enrichment *p* value was <1.0e-16 (Figure 2).

## Identification of the HUB genes

The constructed PPI network was then exported to the cytoscape in order to evaluate the hub genes. DMNC, MNC, Degree, EPC, Bottleneck, Eccentricity, Closeness, Radiality, Betweenness, Stress, and Clustering methods were used for node ranking and the topology analysis. The top hub genes identified after the comparative analysis were- ACE, CXCL8 (IL-8), ESR1 (Estrogen Receptor 1), GSK3B, MMP9, PTGS2 (COX-2), PTPN1 (PTP1B) (Table 2).

## Gene ontology and pathway enrichment analysis

Significant overrepresentation of pathways linked to glucose metabolism, adipocytokine signaling, angiogenesis, and oxidative stress was shown by KEGG as well as WIKI pathway enrichment analysis. Major regulators of receptor activation and downstream glucose utilization were part of the insulin signaling. Lipid metabolism and inflammatory mediators were included in adipocytokine signaling pathways. Though oxidative stress response pathways demonstrated the activation of natural antioxidant mechanisms, enrichment of HIF-1 and VEGF signaling pathways also indicated involvement in hypoxia-driven vascular responses (Figure 3).

Enriched pathways and associated targets are summarized in the following Table 3.

## ADME analysis

The 14 phytochemicals, for which the diabetes mellitus type 2 related targets were obtained, were then subjected to the ADME analysis using the SwissADME software. All the phytochemicals were found to be lipophilic, having low-molecular-weight with low to zero TPSA (Figure 4). It thus indicates the hydrophobic nature and limited polarity. All compounds were expected to be soluble and have acceptable oral bioavailability (score = 0.55), with the exception of β-sitosterol and 1-triacontanol. Though certain monoterpenes show low anticipated GI absorption, caused by their high lipophilicity and absence of polar functional groups. In contrast to the highly lipophilic sterol and long-chain alcohol, which have poor or insoluble profiles and are not BBB permeant, most compounds are projected to have BBB permeation based on their low TPSA and moderate-to-high LogP values. All molecules exhibit minimum Lipinski violations, no PAINS alerts, and reduced synthetic accessibility, indicating their eligibility as bioactive natural-product leads. CYP inhibition liabilities are generally low, primarily restricted to CYP1A2 or CYP2C19 for a few drugs. The observations are depicted in the following Table 4:

## Protein Target Selection and Preparation

Targets were chosen using two criteria: availability of high-resolution crystallographic structures and relevance to the pathophysiology of diabetes. The following table provides more information about the finalized targets (Table 5):

## Protein Preparation

The RCSB Protein Data Bank (https://www.rcsb.org/) was the source of the crystal structures. Preparation involves the removal

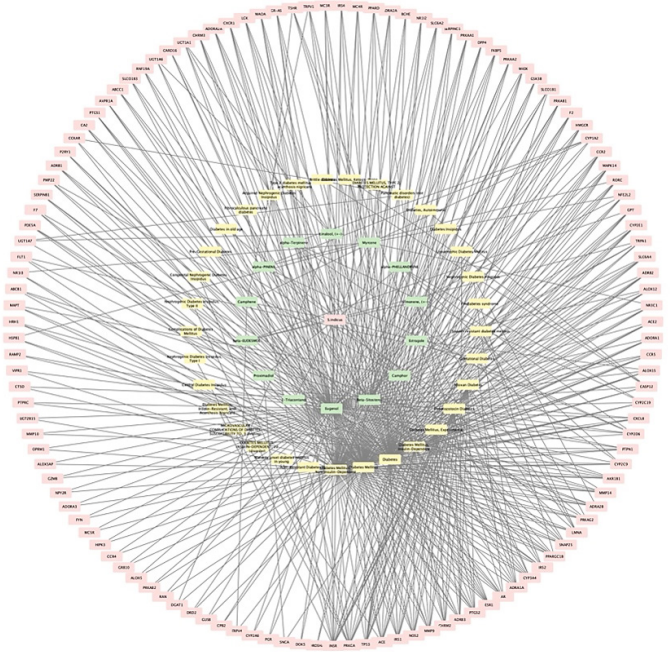

**Figure 1:** Network constructed using Cytoscape.

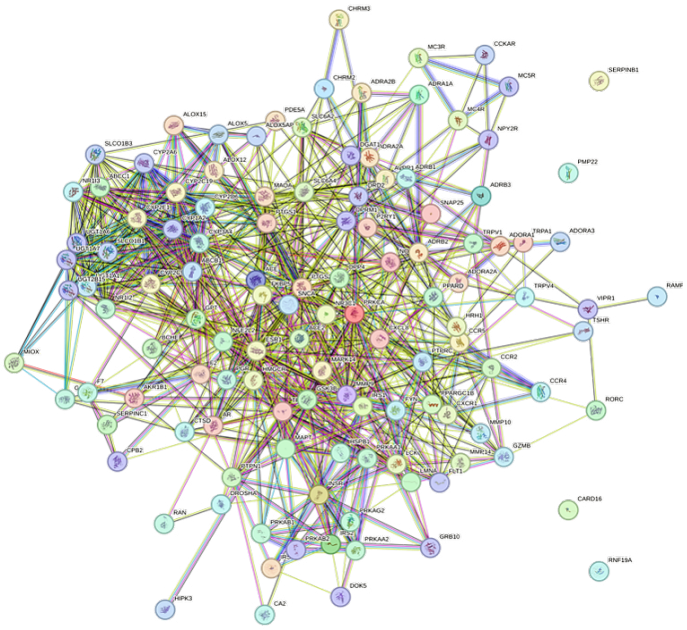

**Figure 2:** PPI interaction studied using the string database.

of water molecules, stripping of co-crystallized ligands (to generate an empty binding pocket), and the addition of polar hydrogen atoms to imitate physiological pH conditions. The preparation was done in the PyMOL 3.1 software (Figure 5).

## Molecular Docking Analysis

Molecular Docking Results of the selected phytochemicals Against Diabetes-Related Protein Targets are given in the following Table 6:

1-Triacontanol and β-sitosterol exhibited quite strong binding affinity to all diabetes-related targets studied, in some cases they even had better or almost as good binding capacity as the reference drugs used for comparison, based on the molecular docking results. More importantly, in comparison to the common drug rosiglitazone, both molecules were predicted to have a higher binding affinity to PPARγ which implies that they could be capable of controlling fat cell formation and improving insulin sensitivity. They also strongly interacted with the angiotensin converting enzyme, which is an indication that they might have a function in lowering the overactivation of the renin-angiotensin system that is associated with diabetic nephropathy. Besides, these two compounds' potential to simulate downstream insulin

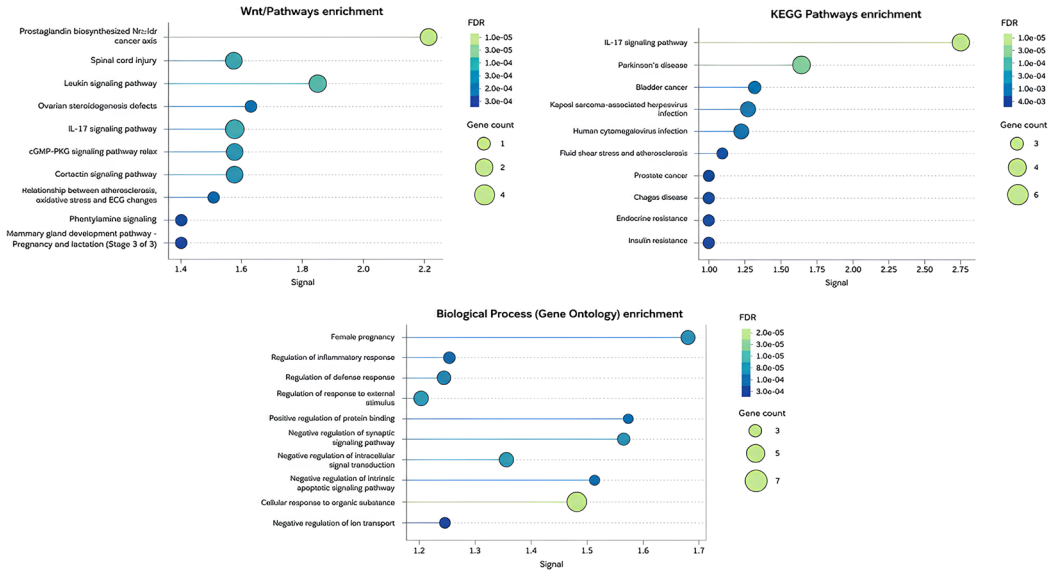


**Figure 3:** Pathway and gene ontology enrichment.

**Table 2: Node ranking based on various methods in CytoHubba.**

| DMNC | MNC | DEGREE | EPC | BOTTLENECK | EcCENTRICITY | CLOSENESS | RADIALITY | BETWEENESS | STRESS | CLUSTERING |
|---|---|---|---|---|---|---|---|---|---|---|
| ALOX12 | ACE | ACE | ACE | CXCL8 | ACE | ACE | ACE | ACE | ACE | ALOX12 |
| ALOX15 | CXCL8 | CXCL8 | CXCL8 | CYP2C9 | AKR1B1 | CXCL8 | CXCL8 | ADRB2 | ADRB2 | ALOX15 |
| AR | CYP2C9 | CYP2C9 | CYP3A4 | CYP3A4 | CXCL8 | CYP3A4 | CYP3A4 | DPP4 | CYP3A4 | F7 |
| CYP2E1 | CYP3A4 | CYP3A4 | ESR1 | DPP4 | CYP3A4 | ESR1 | ESR1 | ESR1 | DPP4 | IRS2 |
| IRS2 | ESR1 | ESR1 | GPT | ESR1 | DPP4 | GPT | GSK3B | GSK3B | ESR1 | IRS4 |
| LCK | GSK3B | GSK3B | GSK3B | GPT | GSK3B | GSK3B | MMP9 | IRS1 | GSK3B | MMP14 |
| MAPK14 | MMP9 | MMP9 | MMP9 | HMGCR | INSR | MMP9 | NR3C1 | MMP9 | IRS1 | NR1I3 |
| NR1I2 | NR3C1 | NR3C1 | NR3C1 | PTGS2 | IRS1 | NR3C1 | PRKCA | PRKCA | MMP9 | PRKAA2 |
| PRKAA2 | PTGS2 | PTGS2 | PTGS2 | SLC6A4 | MMP9 | PTGS2 | PTGS2 | PTGS2 | PTGS2 | PRKAB1 |
| PRKAB1 | TP53 | TP53 | TP53 | TP53 | PRKCA | TP53 | TP53 | TP53 | TP53 | SERPINC1 |

**Table 3: KEGG pathway enrichment and associated genes.**

| Pathway name | KEGG ID | Associated targets | Biological implication |
|---|---|---|---|
| Insulin signaling pathway | hsa04910 | INSR, IRS1, IRS2, GSK3B, PTPN1 | Regulation of glucose uptake and storage |
| Adipocytokine signaling pathway | hsa04920 | PPAR-γ, DPP4, TNF-α | Lipid metabolism and insulin sensitivity |
| HIF-1 signaling pathway | hsa04066 | NOS2, MMP9 | Hypoxia response |
| VEGF signaling pathway | hsa04370 | VEGF-related targets, MMP9 | Angiogenesis regulation |
| Oxidative stress response | - | NFE2L2 (Nrf2) | Antioxidant defense induction |

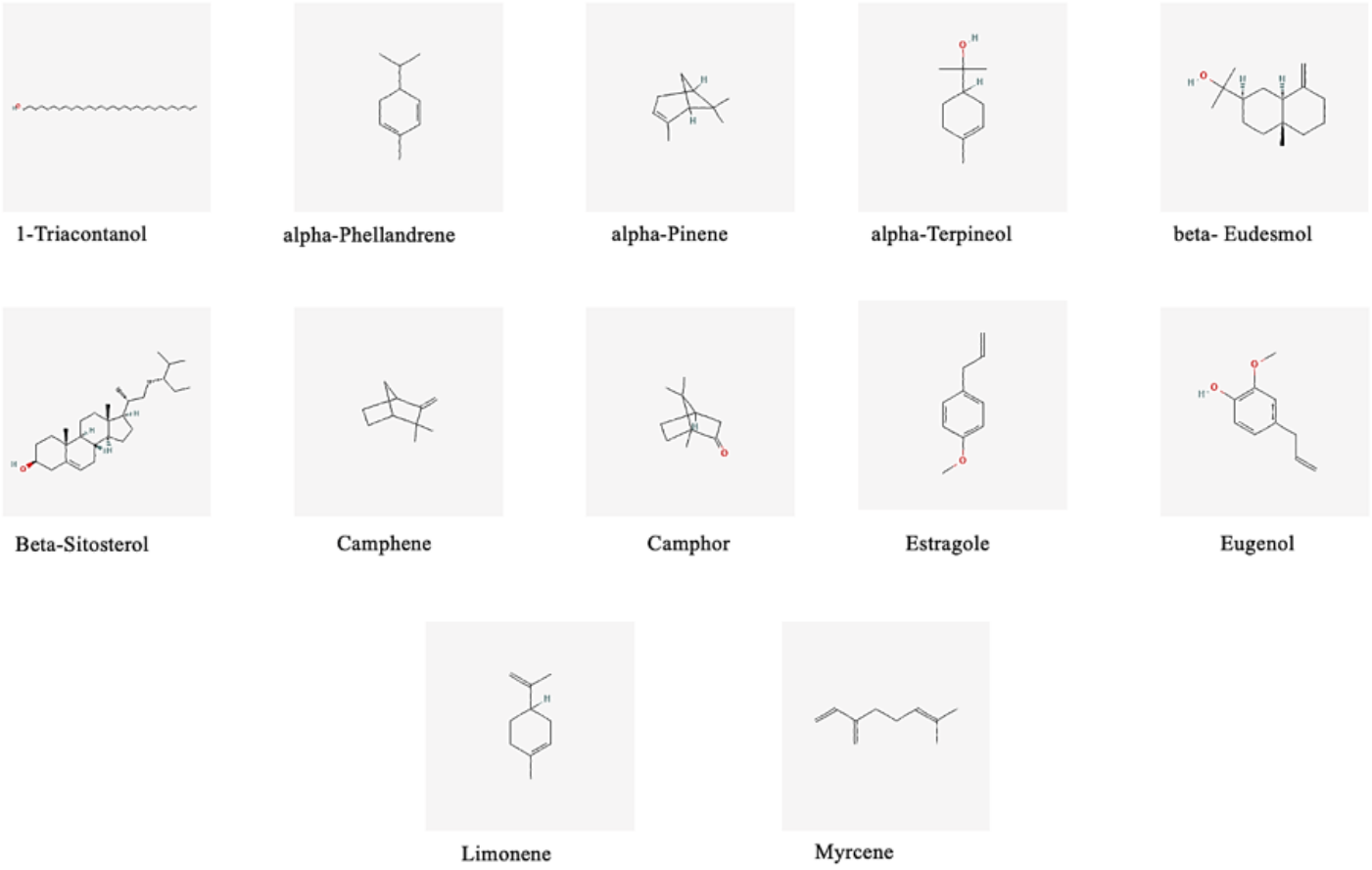


**Figure 4:** 2D structures of the selected phytochemicals.

**Table 4: ADME analysis of the selected phytochemicals.**

| Compound | Formula | MW (g/mol) | TPSA (Å²) | Consensus LogP | Solubility Class | GI Absorption | BBB Permeant | CYP Inhibition* | Lipinski Violations | Bioavailability Score | PAINS Alerts | Synthetic Accessibility |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Eugenol | $C_{10}H_{12}O_2$ | 164.20 | 29.46 | 2.25 | Soluble | High | Yes | CYP1A2 | 0 | 0.55 | 0 | 1.58 |
| β-Eudesmol | $C_{15}H_{26}O$ | 222.37 | 20.23 | 3.60 | Soluble | High | Yes | CYP2C19 | 0 | 0.55 | 0 | 3.38 |
| β-Sitosterol | $C_{29}H_{50}O$ | 414.71 | 20.23 | 7.24 | Poorly soluble | Low | No | None | 0 | 0.55 | 0 | 6.30 |
| 1-Triacontanol | $C_{30}H_{62}O$ | 438.81 | 20.23 | 10.52 | Insoluble | Low | No | None | 0 | 0.55 | 0 | 3.97 |
| Estragole | $C_{10}H_{12}O$ | 148.20 | 9.23 | 2.78 | Soluble | High | Yes | CYP1A2 | 0 | 0.55 | 0 | 1.28 |
| Myrcene | $C_{10}H_{16}$ | 136.23 | 0.00 | 3.43 | Soluble | Low | Yes | None | 0 | 0.55 | 0 | 2.85 |
| Camphor | $C_{10}H_{16}O$ | 152.23 | 17.07 | 2.37 | Soluble | High | Yes | None | 0 | 0.55 | 0 | 3.22 |
| α-Pinene | $C_{10}H_{16}$ | 136.23 | 0.00 | 3.44 | Soluble | Low | Yes | CYP2C19 | 1 | 0.55 | 0 | 4.44 |
| Camphene | $C_{10}H_{16}$ | 136.23 | 0.00 | 3.43 | Soluble | Low | Yes | CYP2C19 | 1 | 0.55 | 0 | 3.50 |
| Limonene (±) | $C_{10}H_{16}$ | 136.23 | 0.00 | 3.37 | Soluble | Low | Yes | CYP2C19 | 0 | 0.55 | 0 | 3.46 |
| α-Terpinene | $C_{10}H_{16}$ | 136.23 | 0.00 | 3.30 | Soluble | Low | Yes | None | 0 | 0.55 | 0 | 3.63 |
| α-Phellandrene | $C_{10}H_{16}$ | 136.23 | 0.00 | 2.97 | Soluble | Low | Yes | None | 0 | 0.55 | 0 | 4.15 |

signaling and trigger glycogen production is consistent with their inhibitory effect on glycogen synthase kinase 3.

Beta sitosterol has shown very strong binding affinity with the EphA4 ligand, binding domain, which might explain one more mechanism through which pancreatic islet cell communication can be restored and hyperglucagonemia regulated. Even though the binding of the phytochemicals to cyclooxygenase 2 was relatively weak, the fact that they constantly bind to it implies that there might be an extra anti, inflammatory effect that could act together with the insulin, sensitizing pathways. In sum, the finding suggests that the controlled phytochemicals, mainly 1, triacontanol and, sitosterol, have the potential to act on different pathways (multi-target/polypharmacology) which is highly desirable in the comprehensive management of diabetes and its various complications (Figure 6).

## DISCUSSION

This present computational study significantly elaborates the mechanistic understanding of the anti-diabetic potential of *Sphaeranthus indicus*. It shows that the array of phytochemicals present in the plant interact with various molecular targets that collectively regulate glucose homeostasis, insulin sensitivity, inflammation and pathways of diabetic complications. Type 2 Diabetes Mellitus (T2DM) is being recognized as a multi-systemic disorder that involves the coordinated dysfunctioning of metabolic, inflammatory, vascular, and neuroendocrine signalling networks, and not only the defect insulin secretion and action. Concerning this complex patho-physiology, the multi-target pharmacological profile revealed by this study is of particular importance. These results corroborate the notion that *S. indicus* mediates its effects through the combined action on various therapeutically relevant targets, thus establishing a molecular rationale for the traditional use of *S. indicus* in diabetes and allied metabolic disorders.

A principal and biologically relevant finding of this work is the extremely strong binding of phytosterols, especially beta-sitosterol and 1-triacontanol to the PPAR. One of the best methods for boosting peripheral insulin sensitivity is still drug-induced activation of PPAR, a crucial regulator of adipocyte development, lipid accumulation, and insulin sensitivity (Bajaj *et al.*, 2007). The docking scores of these sterols that are on a par with or even higher than that of the thiazolidinedione; rosiglitazone indicating that *S. indicus* holds the natural ligands that can modulate this receptor. In fact, phytosterols are generally considered to be selective or partial PPAR agonists, i.e., Selective PPAR Modulators (SPPARMs), which, on the one hand, may keep the insulin, sensitizing effect but, on the other hand, lead to less weight gain, edema, heart failure, etc. as seen in full agonists (Enayati, 2022). This mechanism perfectly corresponds to the *in vitro* data indicating that *S. indicus* treatment improves lipid metabolism and decreases insulin resistance in diabetic animals. The simultaneous GSK3 inhibition potentiates this effect by promoting glycogen synthesis and simulating the downstream insulin signalling, thus directly counteracting insulin resistance in the liver and muscle, which is one of the main features of T2DM (Henriksen and Dokken, 2006).

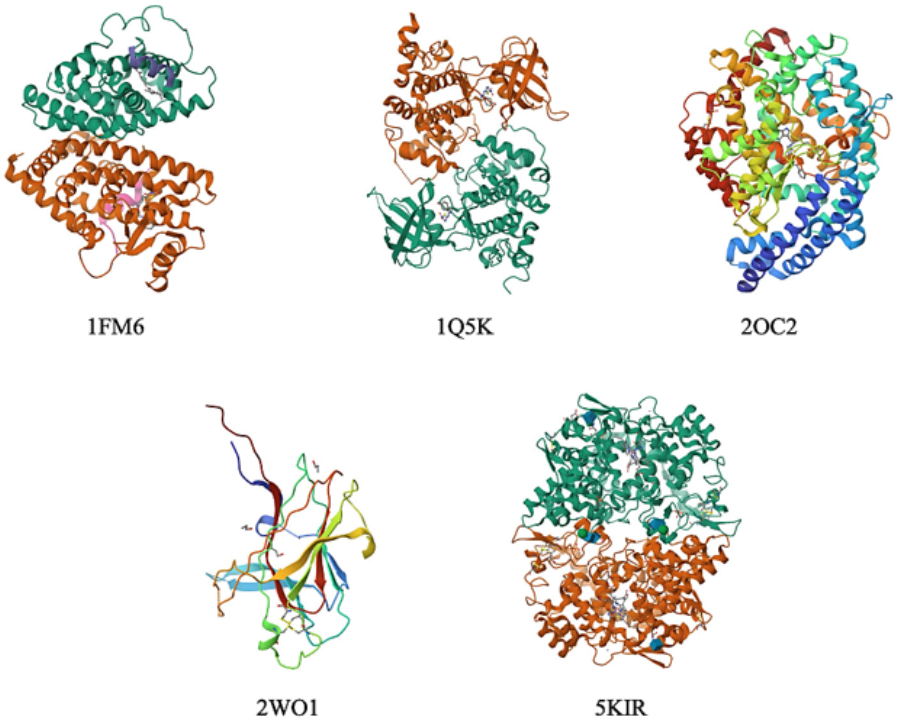


**Figure 5:** Protein structures curated from RCSB PDB database.

**Table 6: Results of the molecular docking studies.**

| Target Protein | PDB ID | Ligand used for the docking | Binding Energy (kcal/mol) | Relative Affinity |
|---|---|---|---|---|
| Peroxisome Proliferator-Activated Receptor-γ (PPAR-γ) | 1FM6 | Rosiglitazone (Control) | −11.06 | Reference |
| | | 1-Triacontanol | −11.80 | Higher than control |
| | | β-Sitosterol | −11.43 | Higher than control |
| | | β-Eudesmol | −8.71 | Moderate |
| Angiotensin-Converting Enzyme (ACE) | 2OC2 | 1-Triacontanol | −11.15 | Very high |
| | | β-Sitosterol | −11.13 | Very high |
| | | β-Eudesmol | −8.18 | Moderate |
| | | Eugenol | −6.73 | Low |
| Glycogen Synthase Kinase-3β (GSK-3β) | 1Q5K | 1-Triacontanol | −11.20 | Very high |
| | | β-Sitosterol | −10.32 | High |
| | | Camphor | −7.85 | Moderate |
| | | β-Eudesmol | −7.79 | Moderate |
| Ephrin Type-A Receptor 4 (EphA4) | 2WO1 | 1-Triacontanol | −11.20 | Very high |
| | | β-Sitosterol | −10.78 | High |
| | | β-Eudesmol | −7.72 | Moderate |
| Cyclooxygenase-2 (COX-2) | 5KIR | β-Sitosterol | −8.00 | Moderate |
| | | 1-Triacontanol | −7.68 | Moderate |
| | | Camphor | −7.38 | Moderate |

**Table 5: Selected targets for the docking studies.**

| Sl. No. | Target Protein | PDB ID | Resolution (Å) | Structural Relevance for Docking | Rationale for Selection in Diabetes |
|---|---|---|---|---|---|
| 1. | Angiotensin-Converting Enzyme (ACE) | 2OC2 | 2 | High-resolution crystal structure with a well-defined catalytic zinc-binding active site suitable for structure-based inhibitor docking. | ACE mediates conversion of angiotensin I to angiotensin II. Its inhibition is clinically beneficial in preventing diabetic nephropathy and cardiovascular remodeling. |
| 2. | Cyclooxygenase-2 (COX-2) | 5KIR | 2.7 | Contains a clearly resolved hydrophobic channel forming the substrate/ inhibitor-binding pocket, enabling reliable docking of anti-inflammatory ligands. | COX-2-driven inflammation contributes to insulin resistance, particularly in adipose tissue during metabolic stress. |
| 3. | Glycogen Synthase Kinase-3 B (GSK3β) | 1Q5K | 1.94 | High-resolution kinase domain with an accessible ATP-binding pocket, making it a robust target for docking and virtual screening studies. | GSK3β negatively regulates glycogen synthesis. Its inhibition enhances insulin signaling and improves glycemic control. |
| 4. | Ephrin Type-A Receptor 4 (EphA4) | 2WO1 | 1.85 (Apo) | Apo-form structure provides a flexible receptor conformation useful for exploring novel ligand-binding modes through docking. | EphA4 signaling modulates glucagon secretion in pancreatic α-cells; dysregulation contributes to hyperglucagonemia in diabetes. |
| 5. | Peroxisome Proliferator-Activated Receptor-γ (PPARγ) | 1FM6 | 2.1 | Well-characterized ligand-binding domain with a spacious hydrophobic cavity, ideal for docking studies of insulin-sensitizing compounds. | PPARγ regulates adipocyte differentiation and glucose homeostasis and is the molecular target of thiazolidinedione antidiabetic drugs. |

Besides the regulation of blood sugar, the potential of *S. indicus* phytochemicals to bind with ACE and COX-2 indicates their wider therapeutic implications, mainly for the treatment of complicated arise due to diabetes mellitus (Malik *et al.*, 1998). One of the major factors driving diabetic nephropathy, endothelial dysfunction, and cardiovascular remodelling is the overactivation of the Renin Angiotensin System (RAS) (Karimi, 2024). The strong predicted binding of beta-sitosterol and 1-triacontanol to ACE suggests a possible pathway through which intrarenal RAS activation could be suppressed, thus supporting renal and vascular function. Moreover, the interaction mode with ACE proposed here which is probably hydrophobic or allosteric, as opposed to classical ACE

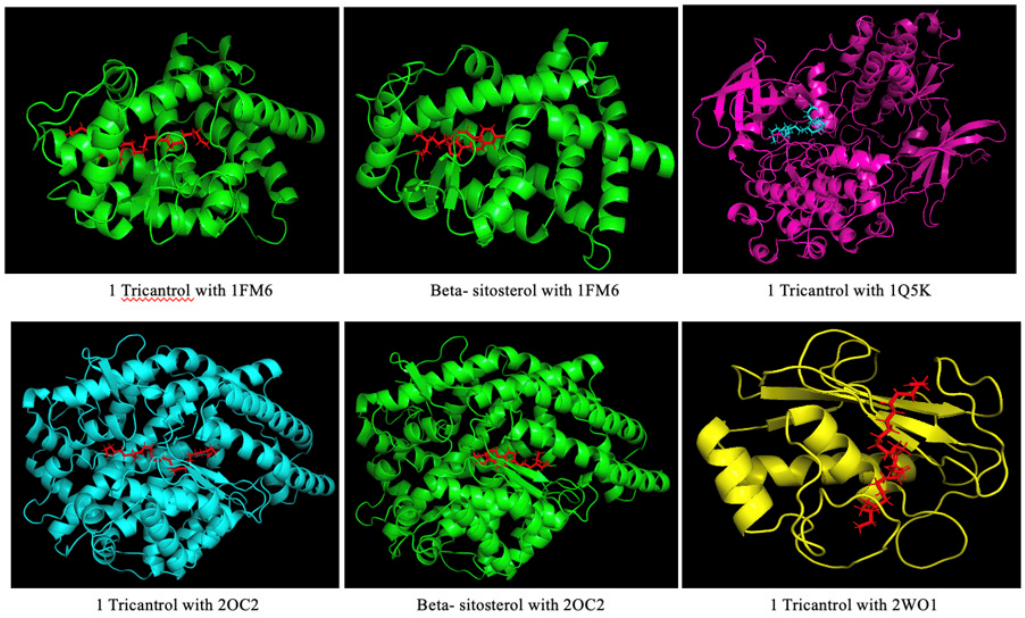


**Figure 6:** Interactions observed after the docking studies.

inhibitors that depend on zinc chelation, might be an additional inhibitory mechanism that goes hand in hand with the traditional use of *S. indicus* as a diuretic and anti-oedematous agent. The simultaneous moderate inhibition of COX-2 strengthens the anti-inflammatory effect, which is very important since chronic low, grade inflammation (meta- inflammation) is one of the major causes of insulin resistance through NFkB and JNK signalling pathways (Acosta-Martinez, 2022). By targeting both metabolic and inflammatory pathways, *S. indicus* is suggested to provide an integrated solution for the underlying causes and complications of T2DM.

This study's discovery of EphA4 as a significant binding partner for *S. indicus* sterols is highly unique and potentially game-changing. EphA4 is fast emerging as a significant role in pancreatic islet cell communication, particularly in the suppression of glucagon release by cells via local signalling (Ng *et al.*, 2022). Hyperglucagonemia has now been identified as a major factor contributing to both fasting and postprandial hyperglycemia in T2DM, and the two-hormone (insulin and glucagon) model of diabetes is becoming accepted as the explanation for the condition (Infante *et al.*, 2025). The goal was to develop a strategy to reduce the excessive secretion of glucagon in diabetics. It is particularly noteworthy that sitosterol is expected to bind to the EphA4 ligand binding domain. This is interesting because it reveals an altogether new channel by which *S. indicus* could impact cell control, reducing improper hepatic glucose synthesis. This pathway is essentially unaffected by most available oral anti-diabetic medications, making the evidence for *S. indicus'* glucose-lowering actions even in advanced disease quite convincing. Modulating EphA4, if confirmed experimentally, could be a viable plant-based strategy for rectifying the insulin, glucagon imbalance that is the main cause of continued hyperglycemia. The network pharmacology study essentially links these molecular-level concepts by disclosing that *S. indicus* phytochemicals affect core genes such as ACE, GSK3B, PTGS2, PTPN1, and CXCL8, which are key parts of insulin signaling, inflammation, oxidative stress, and vascular remodelling pathways. It has been shown that insulin sensitivity might be greatly increased by the inhibition of PTPN1 (PTP1B), which is the negative regulator of insulin receptor phosphorylation, and concurrently by modulating PPAR and GSK3 (Teimouri, 2023). Monoterpenes such as limonene and myrcene cause the activation of Nrf2, dependent targets that are involved in antioxidant defense mechanisms, hinting at the protection of cells from oxidative stress-induced dysfunction, which is an important factor in the progression of the disease.

Taken together, these overlapping pathways scientifically support the Ayurvedic view of *S. indicus* as a Rasayana herb, giving it a new dimension as a multi-target, disease-modifying medication rather than a symptomatic hypoglycemic. While these are tentative predictions, they provide a strong, systems-level reasoning that calls for additional laboratory validations and clinical *S. indicus* translational trials as a complementary or supplementary T2DM treatment.

## CONCLUSION

The computational study of *Sphaeranthus indicus* Linn. offers a comprehensive molecular basis for the traditional use of this Indian medicinal plant in diabetes treatment as per Ayurveda. The employment of both network pharmacology and molecular docking in this research reveals that the effectiveness of the herb is due to it influencing various targets rather than focusing on one mechanism alone.

Among the observed interactions, the two main phytocompounds 1, triacontanol and beta- sitosterol showed a level of binding to

the diabetic key protein targets such as PPAR gamma, GSK3beta, and ACE, quite comparable to that of standard drugs. Another significant finding was the receptor EphA4 with which the phytoconstituents displayed an excellent bond. This indicated the glucagon, lowering effect as the plant's modus operandi, which is one of the scarce mechanisms targeted by the presently available oral hypoglycemic drugs. Moreover, *S. indicus* as a "Rasayana" or rejuvenator mediates the crosstalk between different signaling pathways of metabolism, inflammation, and oxidative stress. Hence, it presents a broad-spectrum therapeutic potential strategy for the treatment of Type 2 Diabetes Mellitus as well as the micro, and macrovascular complications associated with this condition.

## LIMITATIONS

### Computational Nature

The results rest mainly on predictive algorithms and molecular simulations, which might not accurately reflect the complex physiological environment of a living organism.

### Bioavailability Concerns

Even though ADME analysis anticipated acceptable oral bioavailability for most compounds, major candidates such as β-sitosterol and 1, triacontanol exhibited poor aqueous solubility and low gastrointestinal absorption, which may limit their clinical efficacy if used as raw extract.

### Synergistic Complexity

This study has pinpointed individual high-affinity ligands. However, the possible synergistic, antagonistic, or other inter, type interactions among the 57 identified phytochemicals within the total plant extract are still to be elucidated.

### Fixed Protein Models

The rigid protein/ligand docking approach used (via ParDOCK) does not completely take into consideration the dynamic conformational changes (induced fit) of proteins when they bind to ligands.

## FUTURE SCOPE

Pharmacokinetic Optimization: To improve the solubility and gut absorption of very lipophilic compounds such as 1-triacontanol, drug delivery system technologies including nano-formulations could be investigated.

### Glucagon Regulation Studies

Experimental animals with diabetes can be made the subject of a study in which the effect of *S. indicus* on islet cell communication and thereby the set of glucagon secretion through the EphA4 pathway is considered.

Clinical Trials: Translational trials of sufficient thickness shall be required both for the assessment of the safety of *S. indicus* standardized extracts and their efficacy when used as a therapy complementary to the one comprising the conventional drugs administration like Metformin.

### Isolation of Novel Derivatives

The chemical skeletons of the already recognized terpenoids may represent the lead structures for the semi-synthetic development of new anti, diabetic agents possessing perhaps better safety and efficacy profiles.

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## ABBREVIATONS

**1FM6:** PDB ID for Peroxisome Proliferator-Activated Receptor-γ; **1Q5K:** PDB ID for Glycogen Synthase Kinase-3 Beta; **2OC2:** PDB ID for Angiotensin-Converting Enzyme; **2WO1:** PDB ID for Ephrin Type-A Receptor 4;**5KIR:** PDB ID for Cyclooxygenase-2; **ACE:** Angiotensin-Converting Enzyme; **ADME:** Absorption, Distribution, Metabolism, and Excretion; **ADMET:** ADME and Toxicity; **BBB:** Blood-brain barrier; **COX-2:** Cyclooxygenase-2; **$Csp^3$:** Carbon saturation gauge; **CXCL8:** Interleukin-8; **CYP:** Cytochrome P450; **DM:** Diabetes Mellitus; **DMNC:** Density of Maximum Neighborhood Component; **DPP-4:** Dipeptidyl peptidase-4; **EPC:** Edge Percolated Component; **EphA4:** Ephrin Type-A Receptor 4; **ESOL:** Aqueous solubility prediction model; **ESR1:** Estrogen Receptor 1; **GI:** Gastrointestinal; **GLP-1:** Glucagon-like peptide-1; **GSK3β:** Glycogen Synthase Kinase-3 Beta; **HIF-1:** Hypoxia-inducible factor 1; **IDDM:** Insulin-dependent diabetes mellitus (Type 1); **IDF:** International Diabetes Federation;IL-8: Interleukin-8; **IMPPAT:** Indian Medicinal Plants, Phytochemistry and Therapeutics database; **JNK:** c-Jun N-terminal kinase; **KEGG:** Kyoto Encyclopedia of Genes and Genomes; **LogP:** Octanol-water partition coefficient (lipophilicity); **MNC:** Maximum Neighborhood Component; **MW:** Molecular weight; **NF-κB:** Nuclear factor kappa-light-chain-enhancer of activated B cells; **NFE2L2 (Nrf2):** Nuclear factor erythroid 2-related factor 2; **NIDDM:** Non-insulin dependent diabetes mellitus (Type 2); **P-gp:** P-glycoprotein; **PAINS:** Pan-assay interference substances; **PDB:** Protein Data Bank; **PPARγ:** Peroxisome Proliferator-Activated Receptor-gamma; **PPI:** Protein-protein interaction; **PTGS2:** Prostaglandin-EndoperoxideSynthase2(COX-2);**PTP1B:**Protein tyrosine phosphatase 1B; **PTPN1:** Protein tyrosine phosphatase non-receptor type 1; **RAS:** Renin-angiotensin system; ***S. indicus*:** *Sphaeranthus indicus*; **SGLT-2:** Sodium-glucose cotransporter-2;

**SPPARMs:** Selective PPAR modulators; **STRING:** Search Tool for the Retrieval of Interacting Genes/Proteins database; **T2DM:** Type 2 Diabetes Mellitus; **TPSA:** Topological polar surface area; **TZDs:** Thiazolidinediones; **VEGF:** Vascular endothelial growth factor.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHORS' CONTRIBUTIONS

SJ-Conceptualization, Methodology, Analysis, writing draft, Editing manuscript.

## SUMMARY

- 57 phytochemicals identified from *Sphaeranthus indicus*, with 14 compounds targeting 123 T2DM-related genes through network pharmacology analysis.
- Hub genes (ACE, GSK3B, PTGS2, PTPN1, CXCL8) were identified via PPI topology, implicating insulin signaling, inflammation, oxidative stress, and vascular remodeling pathways.
- 1-Triacontanol and β-sitosterol demonstrated superior docking affinity toward key diabetic targets (PPARγ, GSK3β, ACE), in some cases exceeding the reference drug rosiglitazone.
- Predicted strong interaction with EphA4 receptor, suggesting a novel mechanism involving regulation of hyperglucagonemia in T2DM.
- KEGG enrichment revealed modulation of insulin signaling, adipocytokine signaling, HIF-1, VEGF, and oxidative stress pathways, supporting multi-target polypharmacology.
- ADME profiling indicated drug-like properties with minimal Lipinski violations, though high lipophilicity may limit solubility of lead sterols.
- Provides a systems-level molecular rationale for the Ayurvedic use of *S. indicus* as a Rasayana herb in diabetes and its vascular complications.

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