Metabolomics-Driven LC-HRMS Identification and Multi-Target Computational Pharmacology of *Shzygium polyanthum* Bioactives for Mechanism-Based Precision Management of Type 2 Diabetes Mellitus

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Abstract

Type 2 Diabetes Mellitus (T2DM) continues to be a major cause of mortality and metabolic complications in developing nations, highlighting the urgent need for safer and more accessible therapies. Herbal bioactives from *Syzygium polyanthum* (SYPOL) have gained attention due to their traditional use in managing blood glucose levels. Nevertheless, the molecular mechanisms underlying their antidiabetic effects remain poorly understood. This study employed an integrative in silico approach to evaluate the interactions between SYPOL-derived compounds and ten key protein targets involved in T2DM pathogenesis, including HK2, AKT1, PYGL, INSR, PYGM, IGF1R, PPARG, SLC2A1, MAPK3, and GCK. Ethanolic leaf extracts of SYPOL were analyzed using Liquid Chromatography–High Resolution Mass Spectrometry (LC-HRMS) for phytochemical profiling. Detected compounds were screened for structural availability, toxicity, ADME properties, and compliance with Lipinski's Rule of Five prior to molecular docking. From 9.834 detected phytochemical features, 31 compounds met the selection criteria and were docked against the ten diabetes-related targets. The simulations revealed stable interactions within active site regions, primarily driven by hydrogen bonding and favorable binding energies, suggesting potential modulation of glucose metabolism and insulin signaling pathways. ADME profiling indicated acceptable pharmacokinetic properties, with most compounds satisfying Lipinski's parameters. Toxicity prediction showed a 54.83% probability of nephrotoxicity, emphasizing the importance of safety validation in future studies SYPOL contains multi-target bioactive compounds with potential to regulate glucose homeostasis. This computational analysis provides a mechanistic basis for subsequent experimental research and supports the development of SYPOL-based phytotherapeutics for T2DM management.

Keywords: *Computational Pharmacology, Drug-Likeness, Enzyme Inhibitors, Herbal Medicine, Molecular Docking.*

A. INTRODUCTION

The worldwide impact of degenerative conditions, with diabetes mellitus at the forefront, continues to intensify (Renzo et al., 2021). Lifestyle transformations, including urban expansion, elevated sugar intake, and physical inactivity, have accelerated this trajectory (Tseng et al., 2021). Sustained hyperglycemia not only defines the disease but also precipitates downstream complications such as cardiovascular events, renal dysfunction, and nerve damage, all of which elevate mortality risk (Renzo et al., 2021). Global statistics reveal that over 589 million adults currently contend with diabetes, a number expected to surpass 850 million shortly.

Mortality data from 2024 attributes approximately 3.4 million deaths among middle-aged adults to diabetic complications. Developing nations experience the heaviest toll, with Indonesia positioned among the highest-prevalence countries, 20.4 million current cases, projected to exceed 28 million by mid-century (IDF, 2025). These figures underscore the imperative for novel therapeutic approaches that are both effective and widely accessible. Standard T2DM treatments, including metformin, sulfonylureas, and α-glucosidase inhibitors, achieve glycemic control but frequently induce adverse effects ranging from gastrointestinal distress to dangerous hypoglycemia, potentially undermining long-term compliance (Welz et al., 2018; Xie et al., 2023). This limitation has fueled investigation into alternative modalities with potentially superior safety profiles (Quinlan, 2022).

Herbal remedies, deeply embedded in ethnopharmacological traditions, remain integral to diabetes management across numerous developing regions (Pirintsos et al., 2022). Such approaches offer cultural resonance, economic feasibility, and alignment with conservation goals. Historical evidence demonstrates that traditional medicine systems have repeatedly provided blueprints for pharmaceutical innovation (Aware et al., 2022). Syzygium polyanthum has emerged as a species of particular interest. Its flowers have historically been prepared as infusions for blood sugar regulation (Jeyaraj et al., 2021), while leaf decoctions remain a common self-management strategy among T2DM patients (Ismail & Wan Ahmad, 2019; Widodo et al., 2024). Preclinical investigations by (Widyawati et al., 2023) corroborate these traditional applications, demonstrating measurable antihyperglycemic effects in vivo. Nevertheless, the mechanistic basis for these observations remains inadequately characterized.

The potential for SYPOL constituents to simultaneously engage multiple protein targets relevant to glucose homeostasis has not been thoroughly examined. T2DM's complex etiology—spanning insulin signaling defects, pancreatic dysfunction, and metabolic dysregulation—demands analytical frameworks capable of capturing such complexity. Computational strategies offer precisely this capability. Integration of metabolomic profiling with predictive algorithms and interaction analysis enables systematic exploration of compound-target networks.

The present study employs LC-HRMS for comprehensive phytochemical characterization of SYPOL leaves, followed by network pharmacology to elucidate interactions with glucose-regulatory proteins (Gharge et al., 2021). Through this integrative strategy, critical nodes within glucose homeostasis pathways are expected to be identified, and the multi-target mechanisms underlying the antidiabetic activity of SYPOL leaves are intended to be elucidated. By integrating advanced metabolomic profiling with computational systems biology, a data-driven foundation is established for rational phytopharmaceutical development, thereby contributing to the evolving paradigm of multi-target precision ethnopharmacology in the context of T2DM

B. EXPERIMENTAL SECTION

1. Chemicals, Equipment, and Software

All computational analyses were performed on an ASUS Vivobook® (AMD Ryzen 3, 8 GB RAM, Windows 11 Home 64-bit). Software included PyMOL v3.1.0 (RMSD analysis), PyRx v0.8 (AutoDock Vina engine for docking), Discovery Studio Visualizer 2024 (protein preparation and interaction analysis), and Cytoscape v3.10.3 with the CytoHubba plugin (network analysis). Laboratory equipment included a rotary evaporator (Heidolph®), LC-HRMS system (Thermo Scientific™), analytical balance, 0.20 µm nylon membrane filters, and refrigerated storage. Analytical-grade 96% ethanol and HPLC-grade methanol were used throughout.

2. Plant Authentication and Extraction

Vouchered specimens (677/MEDA/2025) of fresh Syzygium polyanthum leaves from the Herbarium Medanense were used in this study. A 100 g portion was macerated with 1 L of 96% ethanol for 72 h at 2–8°C in the dark. Following maceration, the extract was filtered and concentrated under reduced pressure at 40 ± 1°C using a rotary evaporator, then stored at 2–8°C until analysis (Dewijanti et al., 2020).

3. LC-HRMS Phytochemical Profiling

Sample preparation for LC-HRMS involved diluting 100 µL of extract with 900 µL of HPLC-grade methanol and filtering (0.20 µm). Analysis was performed on a Thermo Scientific™ LC-HRMS system, where compounds were tentatively identified using accurate mass and fragmentation patterns (Kusuma et al., 2025; Windarsih et al., 2022).

4. Compound Validation and Screening

Compound validation involved cross-referencing with PubChem. Structures unavailable in PubChem were reconstructed using the RCSB PDB Chemical Sketch Tool and saved as SMILES. Classification with LIPID MAPS was used to retain only secondary metabolites. Subsequent toxicity screening with ProTox-3 selected compounds in classes 4–6, and their protein targets were predicted using SwissADME.

5. Target Identification and Network Analysis

To identify potential targets, protein predictions from SwissADME were intersected with T2DM-related genes retrieved from GeneCards (relevance score ≥15) and OMIM. The overlapping targets, visualized via a Venn Diagram, were then used to construct a protein–protein interaction (PPI) network in STRING. This network, built with a high confidence score of 0.900 for Homo sapiens, was subsequently imported into Cytoscape for topological analysis. Using the CytoHubba plugin, the top 10 hub proteins were identified and prioritized for docking. Structural coordinates for these proteins were downloaded from the RCSB Protein Data Bank, ensuring each

met the quality criteria of a resolution <3 Å, X-ray diffraction determination, human origin, and no mutations.

6. Molecular Docking

Protein structures were prepared using Discovery Studio by removing water and heteroatoms and adding hydrogens. Redocking validation was performed by aligning the grid box to the native ligand; an RMSD <2.0 Å between the redocked and native poses confirmed the protocol's validity (Venkanna et al., 2020). Using PyRx v0.8, docking simulations were performed by centering the grid box on the active site and setting the exhaustiveness to 100. For each ligand, binding affinities (kcal/mol) and conformations were recorded. Subsequently, the highest-ranked poses were visually inspected to identify hydrogen bonds and other crucial interactions with surrounding residues (Chaudhary Kurmi & Karati, 2025).

7. Drug-Likeness, ADME, and Toxicity Prediction

Compliance with Lipinski's Rule of Five (Ro5)—specifically molecular weight < 500 Da, hydrogen bond acceptors <10, hydrogen bond donors <5, and LogP <5—was assessed using the PKCSM server (Ali et al., 2024). Subsequent ADME profiling, covering absorption, distribution, metabolism, and excretion, was also conducted via PKCSM (Olaokun & Zubair, 2023). A comprehensive toxicity evaluation was then carried out using ProTox-3 (Banerjee et al., 2024), encompassing hepatotoxicity, nephrotoxicity, neurotoxicity, cardiotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity.

C. RESULTS AND DISCUSSION

1. Results of Active Compound Identification by LC-HRMS

Untargeted LC-HRMS analysis of SYPOL leaves detected 9.834 compounds within a 25-minute runtime, including α-cadinene, α-cubebene, α-humulene, α-pinene, β-pinene, (+)-linalool, copaene, farnesol, and squalene, with retention times ranging from 5.56 to 16.62 minutes (Fig 1). Previous GC-MS studies have also identified various terpenes in SYPOL leaves, including squalene, α-pinene, linalool, α-tocopherol, nerolidol, and valencene (Ismail & Wan Ahmad, 2019; Rahim et al., 2018; Widyawati et al., 2022). A distinctive characteristic of SYPOL leaves is their fragrant aroma, attributed to their essential oil content. This essential oil, a hallmark component, imparts a potent scent and constitutes the primary source of its bioactivity, making the leaves a culinary flavoring agent. The oil is highly volatile, with its characteristic aroma resulting from a complex mixture of monoterpenes and sesquiterpenes (Mahmoud Dogara, 2021).

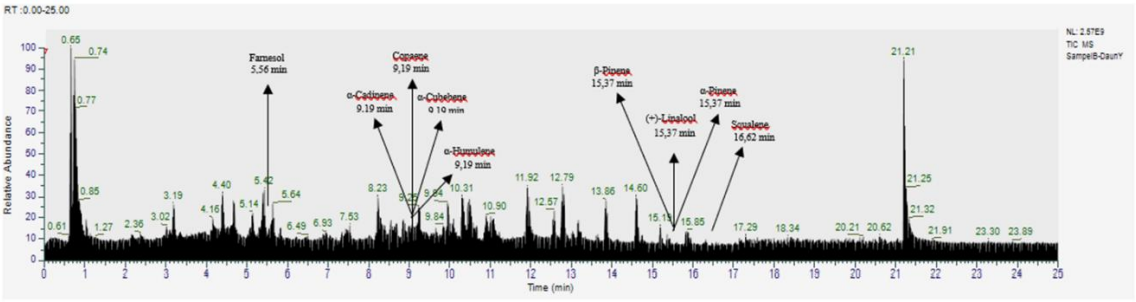

Figure 1. Identification Results of Active Compounds of SYPOL leaves Using LC-

2. Results of Active Compound Screening for SYPOL Leaves

The marked reduction from thousands to a few dozen compounds illustrates a highly selective screening process. Consequently, only 0.33% of the bioactive compounds initially identified in SYPOL leaves satisfied all inclusion criteria and progressed for further analysis. This stringent filtration is detailed in Table 1.

Table 1. Active Compounds of SYPOL Leaves

No.	Name	PubChem ID	Groups	Prediction of Toxicity
1	(+)-Linalool	5281517	Monoterpenes	5
2	6-Hydroxyluteolin 6-xyloside	44258476	Flavones	5
3	9,10-Dihydro-10-(4-hydroxyphenyl)-pyrano(2,3-h)epicatechin-8-one	44157102	Flavonols	5
4	α-Pinene	6654	Monoterpenes	5
5	α-Cubebene	14869	Sesquiterpene	5
6	α-Curcumene	92139	Sesquiterpene	4
7	α-Humulene	5281520	Sesquiterpene	5
8	β-Cadinene	10657	Sesquiterpene	5
9	β-Pinene	14896	Monoterpenes	5
10	Adonixanthin	16061189	Tetraterpene	4
11	Capsorubin	5281229	Tetraterpene	5
12	Cerarvensin	44257651	Flavonols	4
13	Copaene	12303902	Sesquiterpene	5
14	Echinenone	5281236	Tetraterpene	5
15	Farnesol	445070	Sesquiterpene	4
16	Hovetrichoside C	42607791	Aurone	4
17	Kaempferol 7-neohesperidoside	5483905	Flavonols	5
18	Kaempferol-3-O-glucoside-3''-rhamnoside	74124649	Flavonols	5
19	Linderoflavone A	44258651	Flavones	5
20	Luteolin 6-C-glucoside 8-C-arabinoside	3549960	Flavones	4
21	Maritimetin	5281292	Aurone	5
22	Melafolone	5319329	Chalcones	5
23	Morin	5281670	Flavones	5
24	Nothofagin	21722188	Chalcones	5
25	Okanin 4'- (6''-acetylglucoside)	42607561	Chalcones	5
26	Quercetin-4'-glucoside	171380545	Flavonols	5
27	Scutellarein	5281697	Flavones	5
28	Squalene	638072	Triterpenes	6
29	Taxifolin	439533	Flavanones	4

30	Trans-β-Damascenone	5366074	Tetraterpene	5
31	Trans-β-Farnesene	5281517	Sesquiterpene	4

The overlap between SYPOL leaf compounds and the GeneCards and OMIM databases yielded 568 potential target proteins. A subsequent PPI network analysis identified T2DM relevant targets, from which the top 10 hub proteins were selected using Cytoscape with its CytoHubba plugin. The complete selection workflow is depicted in Figure 2.

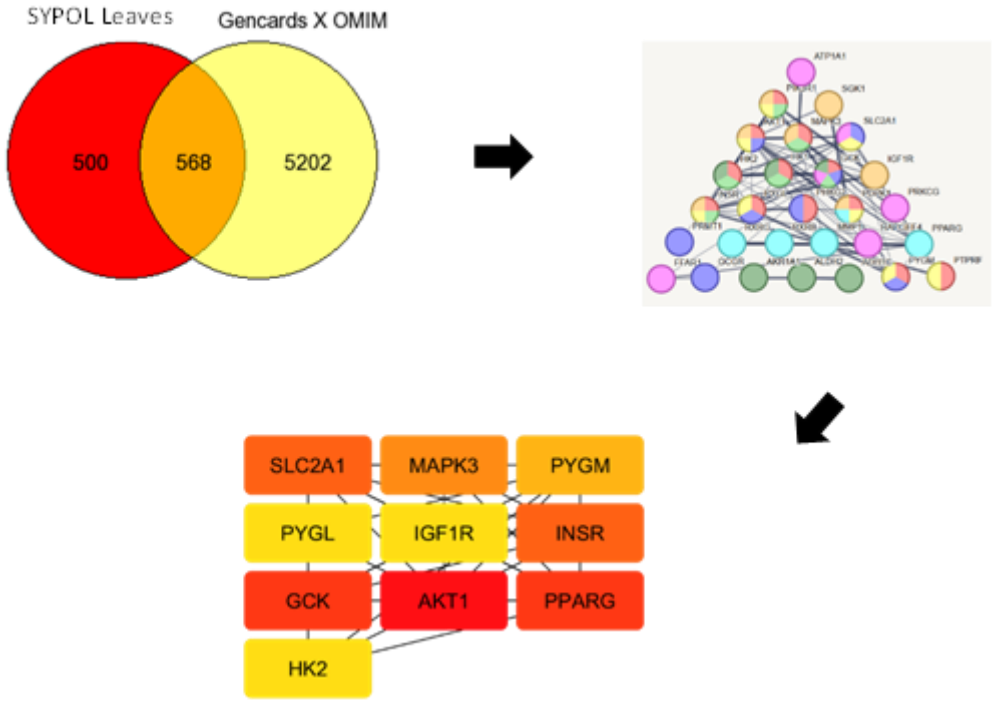

Figure 2. Network Pharmacology Protein Target of SYPOL Leaves; (a) Ovelapping Protein Targets; (b) Networld Pharmacology of Protein Target; (c) Top 10 Protein Target Based on Genes

Ten target proteins for SYPOL leaves were identified using Cytoscape with the 'Degree' ranking method. These targets were subsequently validated through redocking, confirming their suitability based on an acceptable RMSD threshold of < 2 Å (Table 2).

Table 2. Target Proteins of SYPOL Leaves

No	Name	PDB ID	Resolution (Å)	Organism	Method	DR (%)	MFR (%)
1	HK2	2NZT	2,45	Homo sapiens	X-Ray Difraction	4	96
2	AKT1	7NH5	1,90	Homo sapiens	X-Ray Difraction	3	97
3	PYGL	3DDS	1,80	Homo sapiens	X-Ray Difraction	2	98
4	INSR	5E1S	2,26	Homo sapiens	X-Ray Difraction	2	98
5	PYGM	1Z8D	2,30	Homo sapiens	X-Ray Difraction	4	96

6	IGF1R	5FXQ	2,30	Homo sapiens	X-Ray Difraction	3	97
7	PPARG	5YCN	2,15	Homo sapiens	X-Ray Difraction	2	98
8	SLC2A1	6THA	2,40	Homo sapiens	X-Ray Difraction	3	97
9	MAPK3	4QTB	1,40	Homo sapiens	X-Ray Difraction	2	98
10	GCK	5V4X	2,08	Homo sapiens	X-Ray Difraction	3	97

3. Results of Docking Simulation

Simulations were performed between the active compounds from SYPOL leaves and the selected target proteins. The target proteins selected were HK2, AKT1, PYGL, INSR, PYGM, IGF1R, PPARG, SLC2A1, MAPK3 and GCK. The results of the docking simulations are presented in Tab 3. Several bioactive compounds have shown potential interactions with various protein targets through docking simulations. Kaempferol-3-O-rutinoside binds to AKT1 (−11.2 kcal/mol) and PYGL (−10.1 kcal/mol), supporting potential involvement in insulin signaling (Deogratias et al., 2022; Liu et al., 2025). (+)-Linalool interacts via alkyl interactions with residues ILE 48, ALA 69, LEU 173, and VAL 56 on MAPK3 (−13.8 kcal/mol), which plays a role in stabilizing the ligand-protein complex and has the potential to modulate kinase activity (Chen et al., 2022). Cerarvensin from SYPOL leaves binds to PPARG (−10.1 kcal/mol) through π-sulfur contact with MET 348 (Albanese et al., 2022) and pi-alkyl interaction with VAL 83 which may contribute to receptor conformational stabilization and transcriptional modulation (Reza et al., 2025). Okanin 4'-(6''-acetylglucoside) forms a hydrogen bond with THR 213 and a T-shaped interaction with MET 462 on GCK (−8.7 kcal/mol), potentially influencing enzyme activity through ligand orientation stabilization (Rinaldi et al., 2022; Thi et al., 2024). Quercetin-4'-glucoside (−9.3 kcal/mol) forms a hydrogen bond with ASP 1150, which may enhance binding affinity to the receptor (Thi et al., 2024). Adonixanthin forms pi-alkyl contacts with LYS 191 and HIS 57, contributing to ligand-protein complex stabilization (Reza et al., 2025). 9,10-Dihydro-10-(4-hydroxyphenyl)-pyrano(2,3-h)epicatechin-8-one exhibits a donor–donor interaction with ARG 242 on PYGM (−9.4 kcal/mol), which may support isoform selectivity among glycogen phosphorylases (Irannejad et al., 2020), as well as a π-sigma interaction with a MET residue on IGF1R that may help maintain functional ligand orientation within the binding site (Irham et al., 2025). Collectively, these non-covalent interactions contribute to complex stabilization, enhanced affinity, and potential modulation of protein target activity.

SYPOL-derived metabolites exhibit a broad but modest affinity for multiple targets, suggesting multi-target modulation rather than potent single-pathway inhibition—a profile that aligns with the interconnected nature of T2DM pathophysiology, including insulin signaling, glycogen metabolism, and transcriptional regulation. However, molecular docking only predicts structural

compatibility, not biological activity. Key factors such as bioavailability, metabolic transformation (e.g., deglycosylation or conjugation of glycosylated flavonoids), enzyme kinetics, and cellular permeability remain unexamined. Although SYPOL leaves are traditionally used for glycemic control, concurrent use with standard antidiabetic drugs without medical supervision may pose risks of pharmacodynamic interaction (Moaberfard, 2019). Thus, in vitro, cellular, and in vivo studies are necessary to validate these in silico findings. LC-HRMS enabled the identification of specific active compounds, which were further analyzed via docking simulations. These simulations predicted binding interactions—including covalent bonds—with target proteins, offering structural insights into potential functional mechanisms (Khan et al., 2018). While previous studies have reported the blood glucose-lowering (BGL) effects of SYPOL leaves (Parisa et al., 2019; Widodo et al., 2024; Widyawati et al., 2022), they did not specifically investigate isolated compounds such as cerarvensin. Hence, further research is needed to confirm the efficacy of SYPOL leaves in reducing BGL through compound-specific approaches.

Table 3. Results of Docking Simulation for Active Compounds from SYPOL Leaves

Protein Targets	Compounds	Binding affinity (kcal/mol)	Hydrogen Bond
PYGM	9,10-Dihydro-10-(4-hydroxyphenyl)-pyrano(2,3-h)epicatechin-8-one	-9,4	GLY 317, PHE 196, ARG 242, ARG 309, TYR 75, ARG 319
IGF1R	9,10-Dihydro-10-(4-hydroxyphenyl)-pyrano(2,3-h)epicatechin-8-one	-7,8	LEU 1005, ALA 1031, VAL 1013, ASP 1153, MET 1142
PPARG	Cerarvensin	-10,1	VAL 83, SER 80, THR 137, TRP 388, GLN 282
SLC2A1	Cerarvensin	-10,1	VAL 83, SER 80, THR 137, TRP 388, GLN 282
MAPK3	(+)-Linalool	-13,8	TYR 81, ALA 52, ARG 84, TYR 53, ILE 73, LYS 71, LYS 131, ILE 48, MET 125, ASP 123, ALA 69, VAL 56, LEU 173, LYS 71
GCK	Okanin 4'- (6"-acetylglucoside)	-8,7	MET 462, VAL 455, LYS 458, VAL 62, TYR 214, SER 64, ARG 63, PRO 66, TRP 99, TYR 61
HK2	Okanin 4'- (6"-acetylglucoside)	-9,5	THR 232, THR 88, SER 415, THR 213, ASP 209, SER 155, ASP 84, SER 449, LYS 418
AKT1	Kaempferol-3-O-glucoside-3''-rhamnoside	-11,2	LEU 210, ASN 204, TRP 80, LEU 264, VAL 270, LYS 268, GLN 79, ASP 292, ASN 53
PYGL	Adonixanthin	-9,8	GLU 1162, LYS 191, HIS 57, HIS 34, ARG 33, HIS 34

INSR	Quercetin-4'-glucoside	-9,3	HIS 1081, ALA 1080, LEU 1002, MET 1079, ALA 1028, MET 1139, ASP 1150, VAL 1010

The docking results of the active compound against the protein target are provided in the supplementary files.

4. Results of Ro5 Prediction for Active Compounds of SYPOL Leaves

Ro5 compliance was assessed for 31 bioactive compounds from SYPOL leaves (Table 4). Among these, luteolin 6-C-glucoside 8-C-arabinoside exhibited the highest molecular weight at 610.521 Dalton.

Table 4. Ro5 of Active Compounds from SYPOL Leaves

No	Compounds	Ro5			
		MW	HBA	HBD	Log P
1	(+)-Linalool	154,253	1	1	2,6698
2	6-Hydroxyluteolin 6-xyloside	434,353	11	7	0,1002
3	9,10-Dihydro-10-(4-hydroxyphenyl)-pyrano(2,3-h)epicatechin-8-one	436,416	8	5	2,9871
4	α-Pinene	136,238	0	0	2,9987
5	α-Cubebene	204,357	0	0	4,2709
6	α-Curcumene	202,341	0	0	4,84492
7	α-Humulene	204,357	0	0	5,0354
8	β-Cadinene	204,357	0	0	4,5811
9	β-Pinene	136,238	0	0	2,9987
10	Adonixanthin	582,869	3	2	9,7264
11	Capsorubin	600,884	4	2	9,0652
12	Cerarvensin	550,871	1	0	11,7848
13	Copaene	204,357	0	0	4,2709
14	Echinenone	550,871	1	0	11,7848
15	Farnesol	222,372	1	1	4,3979
16	Hovetrichoside C	450,396	11	7	-1,12171
17	Kaempferol 7-neohesperidoside	594,522	15	9	-1,3927
18	Kaempferol-3-O-glucoside-3''-rhamnoside	594,522	15	9	-1,3927
19	Linderoflavone A	358,302	8	2	2,6171
20	Luteolin 6-C-glucoside 8-C-arabinoside	610,521	16	12	-2,6878
21	Maritimetin	370,313	8	0	2,9346
22	Melafolone	400,427	7	2	3,9626
23	Morin	302,238	7	5	1,988
24	Nothofagin	436,413	10	8	-0,1606
25	Okanin 4'- (6''-acetylglucoside)	492,433	12	7	0,1546
26	Quercetin-4'-glucoside	464,379	12	8	-0,5389
27	Scutellarein	286,239	6	4	2,2824
28	Squalene	410,73	0	0	10,605
29	Taxifolin	304,254	7	5	1,1863
30	Trans-β-damascenone	190,286	1	0	3,4342
31	Trans-β-Farnesene	204,357	0	0	5,2015

The Ro5, introduced by Christopher A. Lipinski in 1997, remains a fundamental guideline in drug design for predicting the oral bioavailability of small molecules based on their physicochemical properties (Zheng et al., 2025). It is widely regarded as the most relevant and accurate screening tool for this purpose (Ojuka et al., 2023). The rule is named for its key numerical thresholds—molecular weight <500 Da, Log P <5, hydrogen bond donors <5, and hydrogen bond acceptors <10—all of which are multiples of five (Ali et al., 2024; Pollastri, 2010).

These criteria serve as an initial filter: molecular weight under 500 Da facilitates membrane permeability, Log P below 5 ensures optimal lipophilicity, and limited hydrogen bond donors and acceptors prevent impaired lipid membrane penetration (Ali et al., 2024). Compounds satisfying all four Ro5 criteria are more likely to exhibit good oral bioavailability and be efficiently absorbed through the gastrointestinal tract to reach their biological targets (Ashraf et al., 2021). Copaene compounds isolated from SYPOL leaves meet all Ro5 requirements, including molecular weight, Log P, hydrogen bond donors, and hydrogen bond acceptors. Therefore, they are predicted to be promising novel candidates for alternative T2DM therapy. However, comprehensive follow-up research utilizing in vitro and in vivo approaches remains essential to thoroughly analyze their safety and efficacy profiles before therapeutic application can be considered.

5. Predicton of Pharmacokinetic Properties for Active Compounds from SYPOL Leaves

This study evaluated the ADME properties of active compounds from SYPOL leaves to assess their pharmacokinetic potential (Tab 5). In terms of absorption, linderoflavone A exhibited high absorption (98.669%) (Rhabori et al., 2025), which is favorable for ensuring sufficient compound reaches systemic circulation. Cerarvensin demonstrated sparingly soluble properties with a log S value of 7.274 mol/L (Sanober & Agarwal, 2021), indicating limited aqueous solubility that may affect dissolution. α-Curcumene showed moderate Caco-2 permeability (1.537×10^{-6} cm/s) (Kus et al., 2023), suggesting reasonable intestinal absorption capacity. Regarding distribution, 6-Hydroxyluteolin 6-xyloside exhibited high tissue distribution (VDss 1.851 log L/kg) (Silva et al., 2023), indicating good ability to reach extravascular targets, while cerarvensin heptapeptide remained largely confined to plasma (VDss 0.035 log L/kg) (Silva et al., 2023), which may limit tissue penetration. For plasma protein binding, (+)-linalool showed low binding (FU 48.4%) (Ma et al., 2021), meaning a larger free fraction is pharmacologically available, whereas linderoflavone A exhibited high binding (FU 0.1%) (Ma et al., 2021), potentially reducing free drug concentration. In metabolism evaluation, α-Cubebene was identified as a CYP1A2 inhibitor (Zhao et al., 2021), which could affect co-administered drug metabolism, and none of the compounds were substrates for OCT2 (Noorlander et al., 2023), suggesting a favorable safety profile for patients with renal impairment. Collectively, favorable ADME parameters—such as high absorption, optimal distribution, appropriate protein binding, and minimal drug interaction liability—enhance the likelihood of a

compound achieving therapeutic concentrations at target sites with reduced toxicity risk, supporting further development of SYPOL-derived compounds as potential therapeutic agents (Verma et al., 2025).

Table 5. ADME Prediction for Active Compounds of SYPOL Leaves

	Absorption							Distribution				Metabolism						Excretion	
	Parameters																		
Compounds	Water solubility (Log mol/L)	Caco2 permeability (10^{-6} cm/s)	GI absorption	Skin permeability log Kp (Cm/s)	P-gp subtrate (Yes/No)	P-gp I inhibitor (Yes/No)	P-gp II (Yes/No)	VDss (log L/kg)	Fraction unbond	BBB permeant (Log BB)	CNS permeability (Log PS)	CYP2C9 substrate (Yes/No)	CYP3A4 substrate (Yes/No)	CYP1A2 inhibitor(Yes/No)	CYP2C19 inhibitor (Yes/No)	CYP2C9 inhibitor(Yes/No)	CYP2D6 inhibitor (Yes/No)	CYP3A4 inhibitor(Yes/No)	Total renal clearance (Log ml/min/kg)	Renal OCT2 Substrate
(+)-Linalool	-2,612	1,493	93,163	-1,737	No	No	No	0,152	0,484	0,598	-2,339	No	No	No	No	No	No	No	0,446	No
6-Hydroxyluteolin 6-xyloside	-2,906	0,199	48,162	-2,735	yes	No	No	1,851	0,137	-1,673	-4,212	No	No	No	No	No	No	No	0,37	No
9,10-Dihydro-10-(4-hydroxyphenyl)-pyrano(2,3-h)epicatechin-8-one	-3,118	-0,154	78,186	-2,735	yes	yes	yes	-0,439	0,001	-1,373	-3,367	No	yes	No	No	No	No	yes	0,136	No
α-Pinene	-3,733	1,38	96,041	-1,827	No	No	No	0,667	0,425	0,791	-2,201	No	No	No	No	No	No	No	0,043	No
α-Cubebene	-5,968	1,389	95,964	-1,997	No	No	No	0,717	0,114	0,86	-1,552	No	Yes	Yes	No	No	No	No	0,98	No
α-curcumene	-5,962	1,537	93,29	-1,477	No	No	No	1,089	0,015	0,593	-1,554	No	Yes	Yes	No	No	No	No	1,511	No
α-Humulene	-5,191	1,421	94,682	-1,739	Yes	No	No	0,505	0,347	0,663	-2,555	No	No	No	No	No	No	No	1,282	No
β-Cadinene	-5,816	1,434	97,155	-1,481	No	No	No	0,69	0,199	0,789	-1,955	No	No	No	No	No	No	No	1,177	No

β-Pinene	-4,191	1,385	95,525	-1,653	No	No	No	0,685	0,35	0,818	-1,857	No	No	No	No	No	No	No	0,03	No
Adonixanthin	-6,634	1,239	90,741	-2,738	Yes	No	Yes	-0,504	0	-0,531	-1,187	No	Yes	No	No	No	No	No	0,881	No
Capsorubin	-6,336	0,42	91,047	-2.765	No	No	Yes	-0,752	0	-0,094	-1,664	No	Yes	No	No	No	No	No	0,957	No
Cerarvensin	-7,274	1,243	93,0,77	-2,738	No	No	Yes	0,035	0	0,797	-1,192	No	Yes	No	No	No	No	No	0,891	No
Copaene	-5,705	1,374	96,221	-2,225	No	No	No	0,806	0,115	0,887	-1,659	No	Yes	Yes	No	No	No	No	0,95	No
Echinenone	-7,274	1,243	93,077	-2,738	No	No	Yes	0,035	0	0,797	-1,192	No	Yes	No	No	No	No	No	0,891	No
Farnesol	-5,393	1,495	91,531	-1,514	No	No	No	0,36	0,206	0,66	-1,933	No	No	No	No	No	No	No	1,754	No
Hovetrichoside C	-2,496	0,458	41,248	-2,735	Yes	No	No	0,773	0,271	-1,093	-4,157	No	No	No	No	No	No	No	-0,071	No
Kaempferol 7-neohesperidoside	-2,9	-1,069	19,578	-2,735	Yes	No	No	1,293	0,161	-1,807	-4,999	No	No	No	No	No	No	No	-0,166	No
Kaempferol-3-O-glucoside-3''-rhamnoside	-2,902	-0,478	30,203	-2,735	Yes	No	No	0,074	0,213	-1,932	-5,604	No	No	No	No	No	No	No	0,06	No
Linderofolavone A	-3,239	0,471	98,669	-2,742	Yes	No	Yes	-0,156	0,001	-0,812	-3,393	No	Yes	Yes	No	No	No	Yes	0,462	No
Luteolin 6-C-glucoside 8-C-arabinoside	-2,881	-1,402	11,639	-2,735	Yes	No	No	0,733	0,269	-2,114	-4,957	No	No	No	No	No	No	No	-0,333	No
Maritimetin	-3,864	1,233	98,116	-2,742	No	Yes	Yes	-0,445	0,123	-1,115	-3,38	No	Yes	Yes	No	No	No	No	0,356	No
Melafolone	-4,515	0,125	84,526	-2,754	Yes	Yes	Yes	-0,124	0	-0,487	-2,974	No	Yes	No	Yes	yes	No	yes	0,188	No
Morin	-2,978	-0,294	75,408	-2,735	Yes	No	No	1,229	0,214	-1,18	-3,389	No	No	Yes	No	No	No	No	0,486	No

Nothofagin	-2,817	0,933	46,385	-2,735	Yes	No	No	1,226	0,314	-1,334	-3,982	No	No	No	No	No	No	No	-0,071	No
Okanin 4'- (6"-acetylglucoside)	-2,965	-0,105	44,408	-2,735	Yes	Yes	No	2,119	0,198	-1,831	-4,183	No	No	No	No	No	No	No	-0,018	No
Quercetin-4'-glucoside	-2,908	-2,74	35,947	-2,735	Yes	No	No	1,999	0,252	-1,698	-4,104	No	No	No	No	No	No	No	0,38	No
Scutellarein	-3,063	0,936	70,092	-2,736	Yes	No	No	-0,046	0,111	-1,267	-2,488	No	No	Yes	No	Yes	No	No	0,625	No
Squalene	-8,401	1,193	89,002	-2,763	No	No	Yes	0,35	0	0,965	-0,935	No	Yes	No	No	No	No	No	1,791	No
Taxifolin	-3,042	0,924	64,709	-2,735	Yes	No	No	1,638	0,32	-0,725	-3,198	No	No	No	No	No	No	No	-0,078	No
Trans-β-damascenone	-3,505	1,229	96,897	-1,803	No	No	No	0,265	0,402	0,604	-2,345	No	No	No	No	No	No	No	0,265	No
Trans-β-Farnesene	-6,956	1,405	93,432	-1,281	No	No	No	0,574	0,149	0,835	-1,669	No	No	No	No	No	No	No	1,832	No

6. Results of Toxicity Prediction for Active Compounds of SYPOL Leaves

Nephrotoxicity refers to kidney damage caused by exposure to heavy metals, medications, or specific chemical compounds. The kidneys function to filter the blood, allowing harmful substances to be excreted in urine (Kwiatkowska et al., 2021). However, continuous exposure can damage renal structures such as the glomeruli. This results in a decreased glomerular filtration rate, potentially leading to acute or chronic kidney failure. Common symptoms of nephrotoxicity include sepsis, DM and hypertension (Džidić-Krivić et al., 2024).

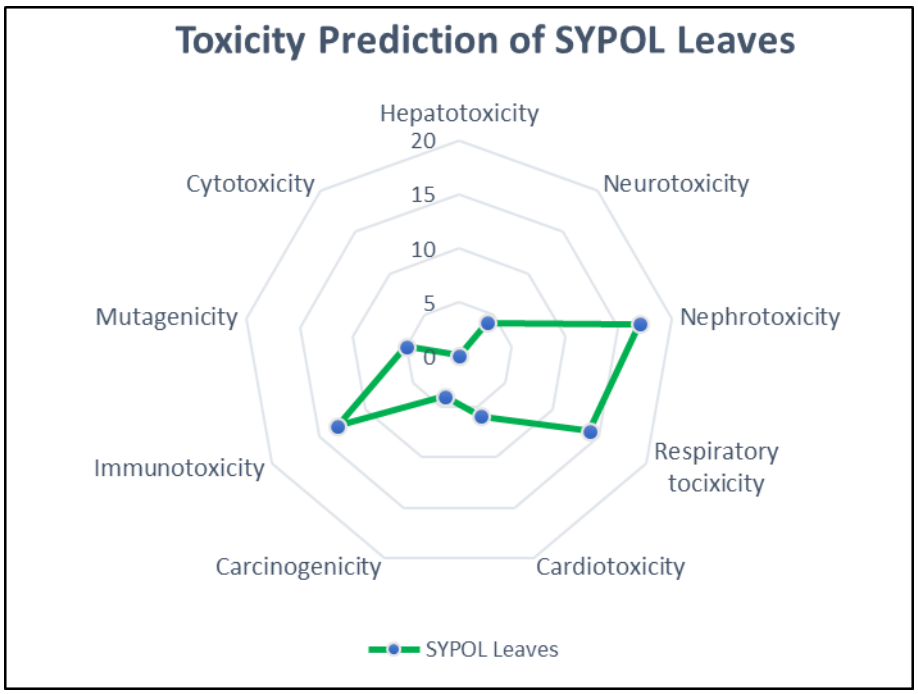

Figure 3. Toxicity Prediction for Active Compounds of SYPOL Leaves

Predictions from SwissaADME regarding the respiratory toxicity of SYPOL leaves compounds should be interpreted cautiously due to methodological limitations. The tool's accuracy may be limited, especially for complex natural products with unusual properties, posing a risk of errors. Variability in predictive power, lack of algorithm customization, and a focus on single-compound evaluation reduce its rselevance for assessing toxicity in herbal mixtures. Moreover, SwissaADME does not offer detailed mechanistic insights into toxicity predictions, so findings should not be considered conclusive without further experimental validation (Nizamuddin et al., 2024). Predicting the toxicity of natural products is essential to ensure safety, reduce research costs and time, and thereby improve drug development efficiency. However, further studies are necessary to conclusively verify the safety of any natural material. In vitro and in vivo approaches are commonly employed to assess the toxic potential of compounds.

D. CONCLUSIONS

T2DM continues to be a major health concern, especially in developing nations. This research identified the phytochemical constituents of SYPOL using LC-HRMS and assessed their potential antidiabetic effects through an integrated in silico approach. A range of metabolites exhibited moderate to strong predicted binding affinities to key proteins involved in glucose regulation—such as HK2, AKT1, PYGL, INSR, PYGM, IGF1R, PPARG, SLC2A1, MAPK3, and GCK—indicating a possible multi-target mechanism of action. Although most compounds satisfied Lipinski's Rule of Five, only a few displayed favorable pharmacokinetic properties, and toxicity predictions suggested a potential risk of nephrotoxicity. These results offer an initial mechanistic insight into SYPOL's antidiabetic potential, but further experimental

confirmation through in vitro and in vivo studies is required to confirm its therapeutic applicability.

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