

Network Pharmacology and Molecular Docking Combined with *in vitro* α -Amylase and α -Glucosidase Assays to Assess Anti-diabetic Properties of *Curcuma longa*

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ABSTRACT

Background: This study investigates the antidiabetic effects of *Curcuma longa* extract using *in vitro* enzyme assays, network pharmacology, and *in silico* molecular docking to elucidate its molecular mechanisms. **Materials and Methods:** From 133 *Curcuma longa* phytochemicals screened via TCMSP, 52 underwent ADMET and toxicity analysis using Protox-3, Superpred, and SwissTargetPrediction. Ethanol-based Soxhlet extraction was performed on the rhizome. Compounds were filtered by ADME/toxicity profiles, and their protein targets were retrieved. Diabetes-related targets from GeneCards were overlapped with compound targets using Venny 2.0, identifying 157 common targets. A Protein-Protein Interaction (PPI) network was constructed in Cytoscape (STRING, confidence ≥ 0.700), with hub targets identified via CytoHubba. Gene ontology and KEGG analyses highlighted key pathways. The network output was validated by molecular docking using CB-DOCK2 and the docking interactions were validated by molecular dynamics simulation using GROMACS. *In vitro* antidiabetic effects were assessed using α -amylase and α -glucosidase assays. **Results:** Six phytochemicals (Campesterol, Stigmasterol, Curcumenol, Curcumol, Curcumin, Procucumadiol) showed favorable ADME/toxicity profiles. From 253 potential targets, 179 were refined, and 3,756 diabetes-related targets (Gene Importance Score $>55\%$) were identified from 20,752. Overlapping revealed 157 common targets, forming a PPI network (186 nodes, 259 edges). Ten hub genes (e.g., AKT1, ESR1, STAT3) were identified, with curcumin showing strong docking interactions with STAT3, AKT1, and ESR1. The molecular docking and MD simulation results indicate a stable Curcumin-STAT3 complex with consistent RMSD, minimal ligand deviation, sustained hydrogen bonds, and stable Rg and SASA over 10 ns. *In vitro* assays demonstrated dose-dependent inhibition of α -amylase and α -glucosidase, comparable to acarbose. **Conclusion:** *Curcuma longa* ethanol extract exhibits antidiabetic effects, supported by network pharmacology, molecular docking, and enzyme assays, highlighting key protein targets and pathways.

Keywords: *Curcuma longa*, Curcumin, Diabetes, Molecular Docking, Network Pharmacology.

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INTRODUCTION

Diabetes mellitus, a long-lasting metabolic disorder featured by hyperglycemia, poses a substantial global health challenge owing to its growing prevalence and accompanying complications, such as cardiovascular diseases, diabetic neuropathy, diabetic nephropathy and diabetic retinopathy. Type 2 Diabetes Mellitus

(T2DM), which accounts for approximately 90% of cases, arises from insulin resistance and decreased insulin secretion, driven by complex pathophysiological mechanisms including oxidative stress, inflammation, and faulty glucose metabolism. Current pharmacotherapies, while effective to some extent, often lead to adverse effects and fail to address the multifaceted nature of T2DM, prompting a growing interest in natural products with multi-target therapeutic potential.¹⁻⁴ Turmeric (*Curcuma longa*), a renowned medicinal herb in Ayurveda and Traditional Chinese Medicine (TCM), is rich in bioactive curcuminoids, including curcumin, which have anti-inflammatory, antioxidant, and hypoglycemic properties.^{5,6} The phytochemicals in turmeric, especially curcumin, have been researched for controlling diabetes owing to their anti-inflammatory, antioxidant, anti-hyperglycemic,



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and insulin-sensitizing properties, promoting blood glucose homeostasis and glucose metabolism.⁷ A randomized controlled experiment found that curcumin supplementation (300 mg/day) in prediabetics delayed type 2 diabetes development by improving beta-cell activity and reducing insulin resistance.⁸ According to a study, curcumin protected against diabetic complications in streptozotocin-induced diabetic mice by lowering oxidative stress indicators (such as malondialdehyde) and raising antioxidant enzyme levels. In streptozotocin-induced diabetic rats, curcumin inhibits the damage that is caused by oxidative stress to the pancreas.^{9,10} Curcumin also exhibits anti-diabetic properties by inducing anti-inflammatory effects. Curcumin reduces the production of pro-inflammatory cytokines such as Tumour Necrosis Factor- α (TNF- α), Interleukin-6 (IL-6), and Monocyte Chemoattractant Protein-1 (MCP-1) by blocking Nuclear Factor- κ B (NF- κ B) activation. By lowering inflammation-induced insulin resistance, this enhances insulin signalling.^{11,12} Although, there are various studies reported on the detailed molecular mechanism of action of *Curcuma longa* and its constituents, especially curcumin, but *Curcuma longa* also contains some other important phytochemicals with anti-diabetic potential and have been studied less. Further, due to the multicomponent nature of the *Curcuma longa* extract, it is very difficult to assign a particular therapeutic effect to a particular phytochemical compound. Further, it is also not clear which of the anti-diabetic mechanisms are operative and what kind of phytochemicals are responsible for each type of antidiabetic mechanisms.

A systems biology-based paradigm called network pharmacology combines experimental and computational methods to comprehend the intricate relationships that exist between bioactive phytochemicals, their molecular targets, and biological pathways. It is especially useful for researching multi-component, multi-target drugs. It considers the plant as a whole rather than relying on a single compound.¹³⁻¹⁶ Network pharmacology helps in constructing a compound-target network to map interactions between the phytochemicals of *Curcuma longa* and their predicted biological targets. This exhaustive network helps to visualise how multiple phytochemicals of an extract act on multiple targets or how a single phytochemical can target multiple biological targets reflecting the synergistic effects of the herb or how a single phytochemical can exert multiple pharmacological effects. An additional network can also be built which involves target-pathway network linking protein targets with biological pathways like anti-inflammatory, antioxidant or anticancer pathways.^{17,18}

This innovative research integrates network pharmacology, *in silico* molecular docking, and MD simulations with *in vitro* experimental validation to elucidate the multifaceted antidiabetic

mechanisms of *Curcuma longa* extract. While earlier reports have explored the therapeutic potential of this plant, the novelty of our approach lies in the synergistic incorporation of network pharmacology to map complex interactions, alongside advanced docking and MD simulations for precise prediction of binding affinities and stability. We systematically profiled its key phytochemicals, identified potential biological targets for each, and constructed a comprehensive compound-target-disease network, further enriched by protein-protein interaction analyses to uncover novel pathways and therapeutic insights.

MATERIALS AND METHODS

Phytochemical screening for drug-like candidates

Phytochemicals from *Curcuma longa* were obtained from the TCMSP database (<https://tcmssp-e.com/>) based on criteria including Molecular Weight (MW) of 200-500, Oral Bioavailability (OB) $\geq 55\%$, Caco-2 permeability ≥ -0.40 , and Drug-Likeness (DL) ≥ 0.18 . The TCMSP database offers detailed information on herbal compounds, their targets, and pharmacokinetic properties, facilitating the selection of bioactive molecules using specified parameters.¹⁹ These phytochemicals were subsequently evaluated for toxicity using the Protox 3.0 online tool to assess hepatotoxicity, carcinogenicity, cytotoxicity, and mutagenicity.²¹ Additionally, the selected compounds underwent further ADMET analysis via ADMET-AI (<https://admet.ai.greenstonebio.com/>) to evaluate physicochemical properties, such as solubility, lipophilicity, and toxicity profiles to confirm their suitability for further studies.

Identification of compound targets of *Curcuma longa*

The SuperPred database (<https://prediction.charite.de/>) was employed to screen potential targets for the identified phytochemicals in *Curcuma longa*. This platform leverages machine learning algorithms to deliver high-confidence target predictions by integrating chemical structure similarity and bioactivity data, with a probability threshold applied to ensure predictive reliability.²¹ To further validate and broaden the scope of target predictions, the SwissTargetPrediction database (<http://www.swisstargetprediction.ch/>) was utilized. This tool estimates potential macromolecular targets of small molecules based on 2D and 3D structural similarities with known ligands, applying a minimum probability threshold of 50%.²² Phytochemicals that met the initial screening criteria were subjected to target identification using SuperPred and SwissTargetPrediction, with a probability filter of $\geq 50\%$. A compound-target network was constructed using Cytoscape (version 3.9.1), an open-source software designed for visualizing complex networks. Network hubs were identified through the CytoHubba plugin, employing the Degree method to rank nodes according to their connectivity within the network.

Identification of disease targets and construction of Protein-Protein Interaction (PPI) network

The GeneCards database (<https://www.genecards.org/>) was utilized to identify targets relevant to breast cancer. This integrative platform consolidates genomic, proteomic, and transcriptomic information, enabling target filtering based on relevance metrics, such as the Gene-Disease Association (Gifts) score, with a threshold set at $\geq 60\%$.²³ The STRING database was employed to construct a Protein-Protein Interaction (PPI) network for overlapping targets, leveraging functional protein associations with a confidence score threshold of 0.700 to ensure reliable network analysis. Shared targets between phytochemicals and breast cancer were determined using the Venny 2.0 online tool. The intersecting targets were subsequently uploaded to the STRING database²⁴ to generate a PPI network with a confidence score of 0.700. This network was imported into Cytoscape (version 3.9.1) for further analysis. The CytoHubba plugin, utilizing the Degree method, was applied to identify hub genes based on their network connectivity.

The Gene Ontology (GO) and KEGG enrichment analysis

The DAVID bioinformatics platform (<https://davidbioinformatics.nih.gov/tools.jsp>) was utilized for Gene Ontology (GO) and pathway enrichment analysis. This tool offers a user-friendly interface for evaluating Biological Process (BP), Cellular Component (CC), Molecular Function (MF), and KEGG pathways, with visualization capabilities for significant pathways.²⁵ The top 10 most significant pathways for BP, CC, MF, and KEGG categories were visualized. Additionally, KEGG pathways were depicted using a Sankey plot to illustrate the relationships between intersecting targets of phytochemicals and breast cancer targets. A comprehensive network integrating plant, compounds, targets, and pathways was constructed using Cytoscape (version 3.9.1).

Molecular docking analysis

Molecular docking between the key phytochemicals and hub targets was performed using CBDOCK2 web server (<https://cadd.labshare.cn/cb-dock2/>).²⁶ This tool employs an advanced docking algorithm that combines cavity detection-guided docking with template-based docking to accurately predict ligand-protein binding affinities. Its intuitive web-based interface enables efficient virtual screening by automatically detecting binding sites and optimizing docking parameters. Protein preparation was performed using BIOVIA Discovery Studio (version 2021), involving the assignment of Gasteiger charges, addition of hydrogen atoms, and removal of water molecules. Docking was carried out using CB-Dock2 with default grid parameters for blind docking of each protein. Binding affinities were computed, and 2D and 3D interaction diagrams were generated using BIOVIA

Discovery Studio to visualize hydrogen bonds, hydrophobic interactions, and other non-covalent interactions.

Molecular Dynamics Simulations

Molecular dynamics simulations of the STAT3-Curcumin complex were performed using GROMACS 2021.6. The CHARMM36 force field optimized the STAT3 structure, while the CGenFF program generated the ligand topology. The complex was placed in a dodecahedron box with TIP3P water, 1 Å from the edge, and neutralized with sodium and chloride ions. Energy minimization used the steepest descent method, maintaining 300 K and 1 bar. A 10 ns simulation produced 1000 frames, from which RMSD, RMSF, Rg, SASA, and hydrogen bond interactions were analyzed.

Chemicals, Reagents and Instrument

95% Ethanol: Shanghai Aladdin Bio-Chem Technology, China; Soxhlet Extractor: Shanghai Jingke Scientific Instrument, China; Hot Air Oven: Shanghai Yiheng Scientific Instruments, China; Refrigerator: Haier, China; Porcine α -Amylase (1 U/mL): Shanghai Yuanye Bio-Technology, China; 3,5-Dinitrosalicylic Acid (DNS): Shanghai Macklin Biochemical, China; 1% Starch Solution: Shanghai Yuanye Bio-Technology, China; Acarbose: Shanghai Yuanye Bio-Technology, China; Sodium Phosphate Buffer (10 mM, pH 7.0): Shanghai Aladdin Bio-Chem Technology, China; Yeast α -Glucosidase (1 U/mL): Shanghai Yuanye Bio-Technology, China; p-Nitrophenyl- α -D-Glucopyranoside (pNPG): Shanghai Macklin Biochemical, China; Sodium Carbonate (0.5 M): Shanghai Aladdin Bio-Chem Technology, China; Deionized Water: In-House Preparation; UV-vis Spectrophotometer (Model V-1800): Shanghai Mapada Instruments, China

Extraction of *Curcuma longa*

The dry rhizomes (100 g) of *Curcuma longa* were finely ground and then added to a Soxhlet extractor and the extraction was performed using ethanol as the solvent, the extraction was performed for 2.30 hr yielding a gummy extract weighing 20 g. The extract was dried in an oven and kept at 4°C in a refrigerator for further analysis.

α -amylase inhibition assay

Stock solutions of rhizomes of *Curcuma longa* ethanol extracts and acarbose were prepared in deionized water. The inhibition of porcine α -amylase activity was assessed using the dinitrosalicylic acid method. A volume of 100 μ L of plant extract or acarbose (ranging from 0.5 to 10 mg/mL) was added to 100 μ L of α -amylase (1 U/mL) and 200 μ L of 10 mM sodium phosphate buffer (pH 7.0), resulting in a final concentration range of 0.5 to 5.0 mg/mL. The mixtures were pre-incubated at 25°C for 20 min, followed by the addition of 100 μ L of 1% starch solution prepared in 10 mM sodium phosphate buffer (pH 6.9). The reaction mixtures were then incubated at 25°C for an additional 15 min. Reactions were terminated by adding 0.5 mL of dinitrosalicylic acid and

heating the mixture in a boiling water bath for 10 min. After cooling to room temperature, the mixtures were diluted 1:5 with deionized water, and absorbance was measured at 540 nm using a spectrophotometer (Shimadzu, Japan). The percentage inhibition of enzyme activity was calculated as described below.

$$\% \text{ Inhibition} = \left[\left(A_{540}^{\text{Control}} - A_{540}^{\text{Treatment}} \right) / A_{540}^{\text{Control}} \right] \times 100$$

wherein A_{540}^{Control} = Absorbance in control sample without plant extract measured at 540 nm

$A_{540}^{\text{Treatment}}$ = Absorbance in treated sample with plant extract measured at 540 nm.

α -Glucosidase Inhibition Assay

The inhibitory effect on α -glucosidase activity was evaluated using yeast α -glucosidase and p-nitrophenyl- α -D-glucopyranoside (pNPG) as a substrate, following the already reported methodology. A 100 μ L aliquot of *Curcuma longa* extract or acarbose (ranging from 0.5 to 10 mg/mL) was combined with 50 μ L of α -glucosidase (1 U/mL) prepared in 0.1 M phosphate buffer (pH 7.0) and 200 μ L of the same buffer, yielding a final concentration range of 0.5 to 5.0 mg/mL. The mixture was pre-incubated at 37°C for 20 min. Subsequently, 10 μ L of 10 mM pNPG, prepared in 0.1 M Phosphate buffer (pH 6.9), was added, and the reaction mixture was incubated at 37°C for an additional 30 min. The reaction was terminated by the addition of 500 μ L of 0.5 M sodium carbonate. Absorbance was measured at 405 nm using a spectrophotometer (Shimadzu, Japan). The percentage inhibition of α -glucosidase activity was calculated as described.

$$\% \text{ Inhibition} = \left[\left(A_{405}^{\text{Control}} - A_{405}^{\text{Treatment}} \right) / A_{405}^{\text{Control}} \right] \times 100$$

wherein A_{405}^{Control} = Absorbance in control sample without plant extract measured at 405 nm

$A_{405}^{\text{Treatment}}$ = Absorbance in treated sample with plant extract measured at 405 nm.

Ethical Statement

Ethical approval was not required for this study as it did not involve human participants or experimental animals.

Statistical Analysis

All experiments were conducted independently at least three times. Data are expressed as Mean $\pm$ Standard Deviation (SD). Statistical significance was determined using one-way Analysis of Variance (ANOVA) followed by Tukey's multiple comparison *post hoc* test, with $p < 0.05$ considered statistically significant.

RESULTS

Initial Screening and Compound Selection

From a total of 52 compounds identified through the TCMSP, a rigorous screening process was applied based on specific criteria including a MW ranging from 200 to 500, Oral Bioavailability (OB) of at least 55%, Caco-2 permeability greater than or equal to -0.40, and Drug-Likeness (DL) of 0.18 or higher. This stringent filtration resulted in only six compounds surviving the initial screening, as detailed in Table 1. These compounds-Campesterol, Stigmasterol, Curcumenol, Curcumol, Curcumin, and Procurcumadiol-were selected for further analysis due to their promising pharmacokinetic profiles, indicating their potential as viable candidates for therapeutic development.

ADMET Property Analysis

The six selected compounds underwent a detailed ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) property analysis using ADMET-AI, with the results visualized in Supplementary Figure 1. Each compound's radar chart illustrates its performance across key parameters: solubility, bioavailability, blood-brain barrier safety, hERG safety (indicating cardiac toxicity risk), and non-toxicity. All six compounds demonstrated favorable profiles, with high scores in solubility and bioavailability, and were deemed blood-brain barrier safe and hERG safe. Notably, Curcumol showed a slight deviation with a non-toxic score of 75, while others like Campesterol and Curcumin maintained scores closer to 100 across most criteria, suggesting a robust safety and efficacy profile for potential drug development.

Target Identification and Network Analysis

Combining target predictions from SuperPred and SwissTargetPrediction, 253 potential targets were initially identified

Table 1: Pharmacokinetic Properties of Selected Compounds: Lists pharmacokinetic properties (Mol ID, Molecule Name, MW, AlogP, Hdon, Hacc, OB %, Caco-2, BBB, DL, FASA-, HL) of six compounds (Stigmasterol, Campesterol, Curcumenol, Curcumol, Procurcumadiol, Curcumin) from 52 TCMSP compounds, filtered by MW 200-500, OB $\geq$ 55%, Caco-2 $\geq$ -0.40, DL $\geq$ 0.18.

Mol ID	Molecule Name	MW	AlogP	Hdon	Hacc	OB (%)	Caco-2	BBB	DL	FASA-	HL
MOL000449	Stigmasterol	412.77	7.64	1	1	43.83	1.44	1	0.76	0.22	5.57
MOL000493	Campesterol	400.76	7.63	1	1	37.58	1.31	0.93	0.71	0	4.71
MOL000901	Curcumenol	234.37	3.27	1	2	87.82	1.14	1.29	0.13	0.25	9.11
MOL000902	Curcumol	236.39	2.79	1	2	103.55	1.12	1.23	0.13	0.25	9.38
MOL000960	Procurcumadiol	250.37	2.06	2	3	69.82	0.43	0.42	0.13	0.32	6.85
MOL000090	Curcumin	368.41	3.36	3	6	5.15	0.5	-0.76	0.41	0.32	

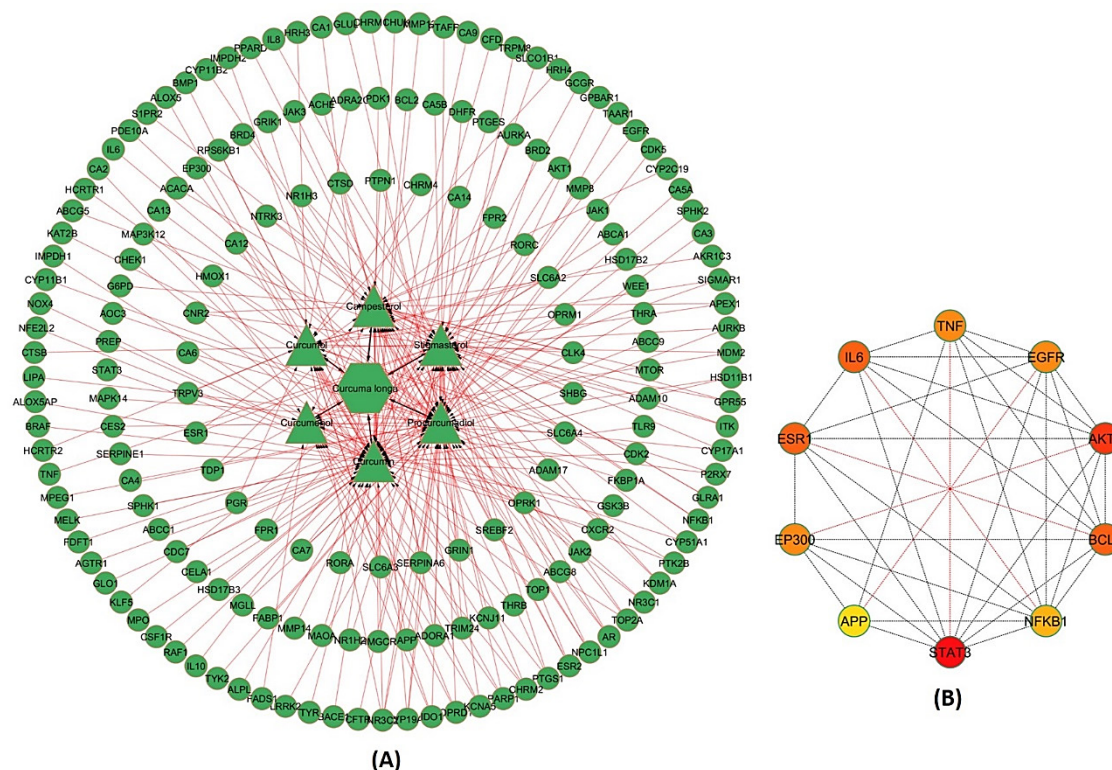


Figure 1: A: Cytoscape PPI Network: Cytoscape visualization of PPI network with 186 nodes and 259 edges. B: Hub Genes: Highlights top 10 hub genes (APP, NFKB1, EP300, TNF, EGFR, ESR1, IL6, BCL2, AKT1, STAT3) by CytoHubba, with AKT1, ESR1, STAT3 as top three.

for the six phytochemicals, which were refined to 179 targets after further screening. Concurrently, 20,752 diabetes-related targets were sourced from the GeneCards database, narrowed down to 3,756 targets with a Gene Importance Score (GIS) above 55%. Cross-referencing the 179 phytochemical targets with the 3,756 diabetes targets revealed 157 overlapping targets (Supplementary Figure 2A). These were analyzed using the STRING database (Supplementary Figure 2B) with a confidence score threshold of 0.400, and the resulting Protein-Protein Interaction (PPI) network was visualized in Cytoscape, yielding 186 nodes and 259 edges (Figure 1A). The CytoHubba plugin highlighted 10 hub genes-APP, NFKB1, EP300, TNF, EGFR, ESR1, IL6, BCL2, AKT1, and STAT3-with AKT1, ESR1, and STAT3 emerging as the top three based on degree centrality (Figure 1B).

Gene ontology outcomes

The Gene Ontology (GO) enrichment analysis revealed significant functional associations of the analyzed gene set across the three GO domains-Biological Process (BP), Cellular Component (CC), and Molecular Function (MF) (Supplementary Figure 3). In the BP category, the most enriched terms included regulation of chronic inflammatory response, negative regulation of cholesterol storage, epigenetic maintenance of chromatin, interleukin-18 production, and sphingosine-1-phosphate receptor signaling, indicating a strong involvement of the genes in immune regulation, lipid metabolism, and transcriptional

control. Notably, enrichment in processes such as positive regulation of nitric oxide synthase biosynthesis and negative regulation of foam cell differentiation further supports a role in vascular inflammation and atherogenesis. Within the CC domain, genes were predominantly localized to the peptidase inhibitor complex, spindle pole centrosome, Wnt signalosome, synaptic cleft, and presynaptic membrane components, suggesting activity in sites critical for cell division, signal transduction, and neuronal communication. The presence of genes in perinuclear endoplasmic reticulum and nuclear structures such as germ cell nuclei implies functions related to protein processing and chromatin organization. In the MF category, the genes demonstrated molecular functions related to peptidase inhibition, ATPase-dependent transmembrane transport, and structural roles in presynaptic membranes, further underscoring their involvement in protease regulation, intracellular transport, and signal reception. The high fold enrichment and significant-log₁₀ (FDR) values observed-particularly for immune and lipid-related processes-highlight the potential of these genes as key regulators in inflammation, metabolic disorders, neurobiology, and possibly cancer progression.

The KEGG pathway enrichment analysis reveals that the analyzed genes are significantly involved in key biological pathways related to inflammation, cell survival, and metabolism. Prominent among these are the PI3K-Akt, TNF, JAK-STAT, mTOR, and HIF-1 signaling pathways, which are crucial for

regulating immune responses, apoptosis, angiogenesis, and cellular proliferation-highlighting their relevance in cancer, autoimmune disorders, and chronic inflammation. Additionally, pathways such as insulin signaling, insulin resistance, and cholesterol metabolism suggest roles in metabolic and cardiovascular diseases. The enrichment of pathways like VEGF signaling, endocrine resistance, alcoholic liver disease, and viral hepatitis further indicates involvement in vascular remodelling, hormonal dysregulation, hepatic damage, and infection-induced inflammation. These results underscore the multifaceted roles of the gene set in interconnected pathological processes, with high

fold enrichment and significance supporting their potential as therapeutic targets or biomarkers (Supplementary Figure 4).

An all-inclusive network linking plants to compounds, targets, and pathways was subsequently generated, providing a comprehensive framework for understanding the therapeutic potential of these compounds in diabetes management (Figure 2A & B).

***In silico* molecular docking results**

The docking results highlight the binding affinity and structural interactions of Curcumin with STAT3, AKT1, and ESR1

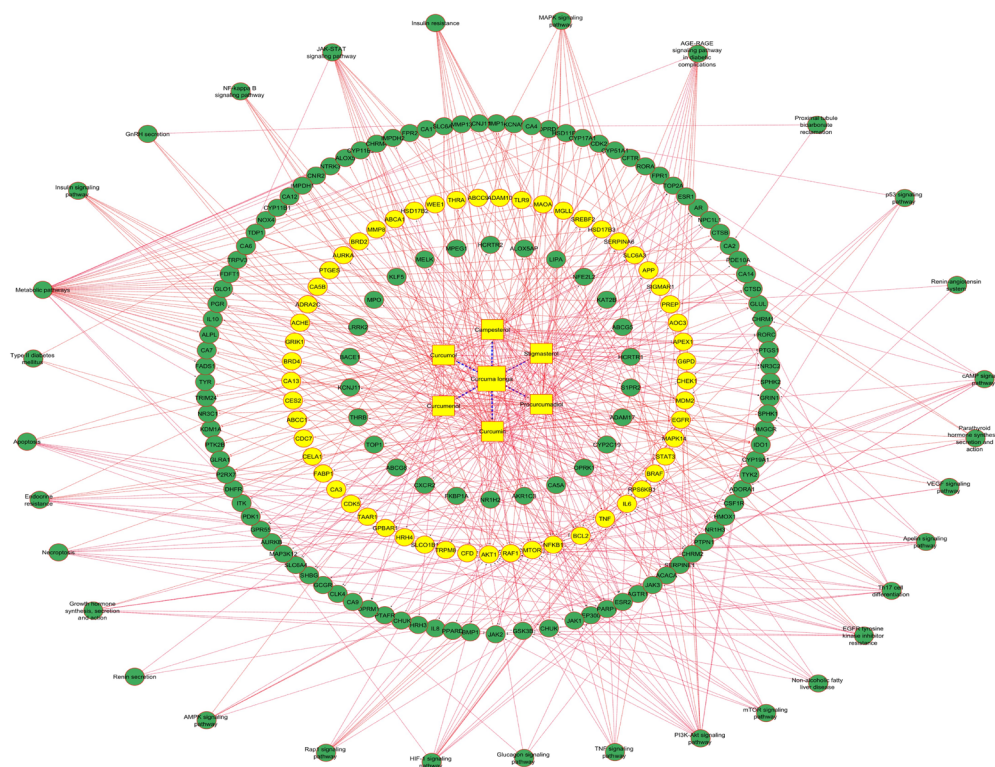


Fig 2A

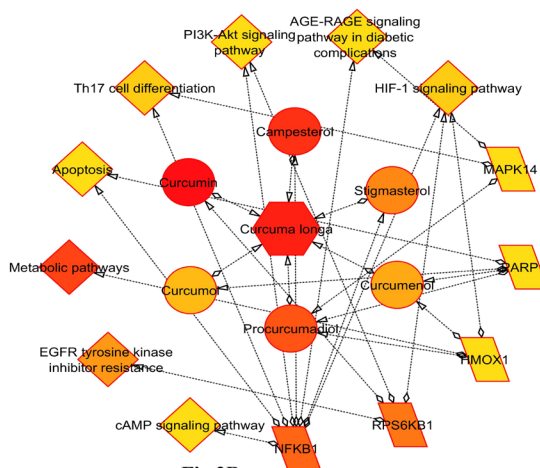


Fig 2B

Figure 2B: 2A and 2B: Plant-Compound-Target-Pathway Network: Illustrates the all-encompassing network linking plants to compounds, targets, and pathways, providing a framework for diabetes therapeutic potential (split into two parts for clarity).

Table 2: Molecular Docking Results of Curcumin with Key Proteins: Details docking outcomes (Ligand-Protein Complex, Docking Score, Cavity Volume, Docking Size, Cavity Size, Contact Residues) for Curcumin with STAT3, AKT1, and ESR1, showing binding affinity and interaction sites.

Ligand-protein complex	Docking score	Cavity volume (Å ³)	Docking size (x, y, z)	Cavity size (x, y, z)	Contact Residues
Curcumin-STAT3 complex	-7.7 kcal/mol	884	26, 26, 26	19, 22, 9	Chain C: TYR22 SER23 ASP24 SER25 PHE26 PRO27 MET28 GLU29 HIS81 ARG84 ARG85 ILE86 GLN88 PHE89 GLN91 SER92 ARG93 Chain D: HIS19 GLN20 TYR22 SER23 ASP24 PHE26 PRO27 MET28 LEU78 HIS81 ASN82 ARG85
Curcumin-AKT1 complex	-6.6 kcal/mol	116	26, 26, 26	7, 8, 6	Chain A: LYS8 GLU9 GLY10 TRP11 LEU12 HIS13 PRO24 ARG25 TYR26 LYS39 GLU40 ARG41 HIS89 VAL90 GLU91 GLU95 ARG96 GLU98 TRP99
Curcumin-ESR1 complex	-6.7 kcal/mol	600	26, 26, 26	11, 13, 12	Chain E: PHE208 ARG211 TYR219 MET220 PRO222 ASP230 LYS231 ARG233 ARG234 LYS235 SER236 CYS237 GLN238 ARG241 Chain F: PHE208 ARG211 SER212 ASN217 ASP218 TYR219 MET220 CYS221 PRO222 THR228 ILE229 ASP230 LYS231 ARG234 LYS235 SER236 CYS237 GLN238 ALA239

proteins, key hub genes in diabetes-related pathways (Table 2). The Curcumin-STAT3 complex exhibits the highest docking score of -7.7 kcal/mol, indicating strong binding, with a cavity volume of 884 Å³ and contact residues across Chains C and D, suggesting extensive interaction sites like TYR22 and ARG85. The Curcumin-AKT1 complex, with a docking score of -6.6 kcal/mol and a smaller cavity volume of 116 Å³, involves Chain A residues such as LYS8 and ARG96, reflecting a more compact binding site. The Curcumin-ESR1 complex, scoring -6.7 kcal/mol with a 600 Å³ cavity, engages Chains E and F, with notable contacts like PHE208 and ARG234, indicating a balanced interaction. Docking sizes (26, 26, 26) are consistent, while cavity sizes vary, reflecting differences in binding pocket dimensions and molecular interactions critical for therapeutic potential (Supplementary Figure 5).

MD simulations

The MD simulation results for the STAT3-Curcumin complex, over 10 ns demonstrate a stable system: the backbone RMSD stabilizes around 0.3-0.5 nm after an initial rise to 0.4 nm, indicating protein conformational equilibrium, while the ligand RMSD remains low at 0.1-0.2 nm with minimal fluctuations, suggesting a tightly bound pose; the protein-ligand RMSD aligns closely with the backbone, reinforcing overall stability (Figure 3A). Figure 3B depicts the Radius of Gyration (Rg) maintaining a steady value, suggesting consistent protein compactness, and the Solvent Accessible Surface Area (SASA) showing minimal variation, indicating stable surface exposure, both supporting the equilibrated complex. Hydrogen bond analysis shows an average of ~1 bond with intermittent peaks to 1.5-2, indicating sustained key interactions, while RMSF values mostly below 0.2 nm reflect a rigid protein core with minor flexible regions (0.3-0.4 nm),

consistent with a well-folded structure. Additionally, together, these metrics confirm a reliable docking pose and stable binding, supporting apigenin's potential as an effective ligand, though extended simulations could enhance trajectory precision.

In vitro experimental results

α-amylase inhibition assay

The ethanol extract of the rhizomes of *Curcuma longa* led to a dose-dependent inhibition of *α*-amylase activity in the concentration range of 0.5 mg/mL to 10 mg/mL (Figure 4A). Acarbose, which is a complex oligosaccharide and functions as a competitive inhibitor of *α*-amylase and *α*-glucosidase, was used alongside the extract to check the inhibition activity of the extract. After 6 mg/mL concentration of extract and acarbose, the % inhibition activity of the enzyme showed only a moderate increase potentially showing a maximum inhibition of 66.2% and 65.2 % for the acarbose and *Curcuma longa* extract respectively.

α-glucosidase inhibition assay

The inhibitory effects of the *Curcuma longa* ethanol extract against *α*-glucosidase enzyme was monitored at varying concentrations (0.5-10 mg/mL range) using acarbose as a standard competitive inhibitor of this enzyme. The *Curcuma longa* extract exhibited a dose-dependent enzyme inhibition which paralleled the inhibitory activity of the standard acarbose. A sharp increase in the inhibitory activity was seen at 4 mg/mL concentration both in case of extract and acarbose. After 4 mg/mL concentration the % inhibition activity was almost found to be unaffected even after using higher concentrations indicating a saturation level. A maximum inhibition of 72.1% and 75.4% was observed for the *Curcuma longa* extract and acarbose respectively (Figure 4B).

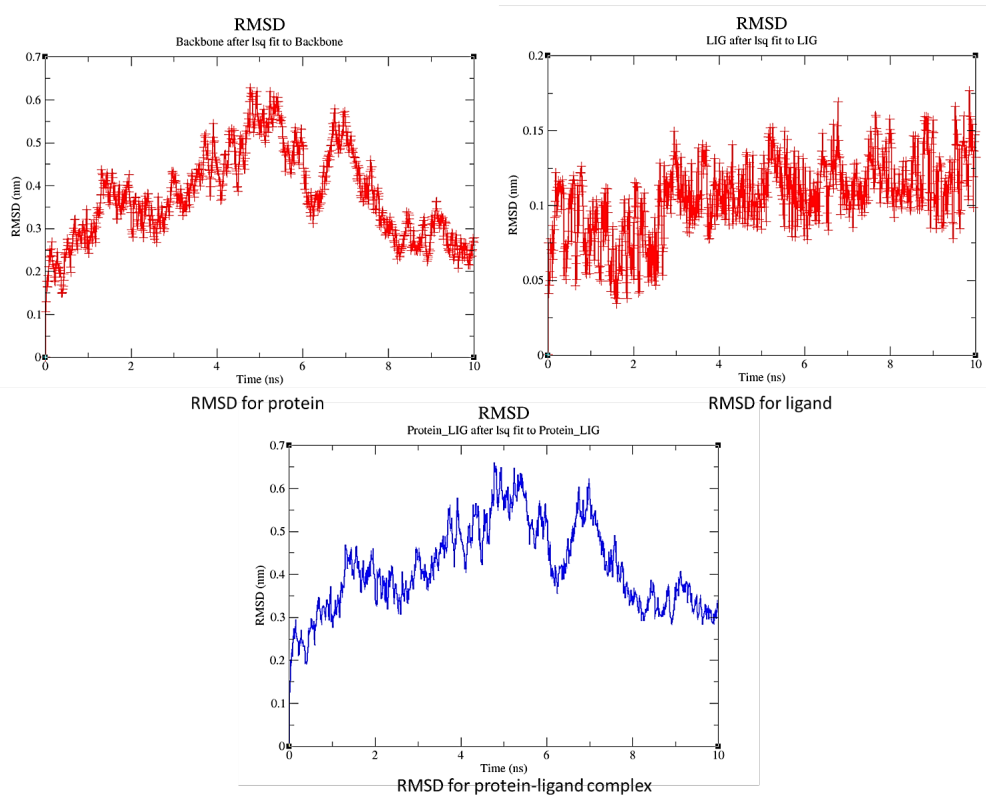


Figure 3A

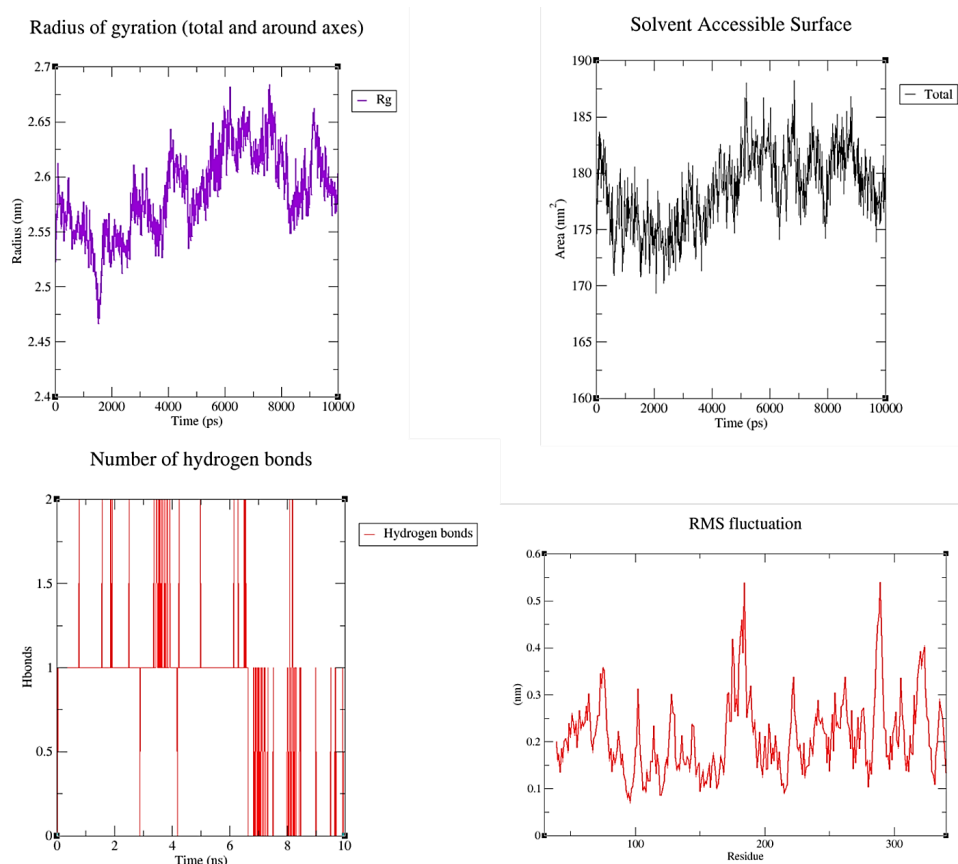


Figure 3B: 3A and 3B: Dynamic analysis over 10 ns, displaying hydrogen bond number (left), RMSF per residue (right), Radius of Gyration, and Solvent Accessible Surface Area, highlighting interaction stability and protein flexibility.

DISCUSSION

The identification of hub genes, APP, NFKB1, EP300, TNF, EGFR, ESR1, IL6, BCL2, AKT1, and STAT3, through the CytoHubba plugin in the Protein-Protein Interaction (PPI) network underscores their central roles in the molecular framework linking phytochemicals to diabetes-related pathways. Among these, AKT1, ESR1, and STAT3 emerge as the top three based on degree centrality, suggesting their pivotal influence in mediating cellular responses. The Gene Ontology (GO) enrichment analysis reveals significant associations across Biological Process (BP), Cellular Component (CC), and Molecular Function (MF) domains, with enriched terms like regulation of chronic inflammatory response, peptidase inhibitor complex, and peptidase inhibition. These findings indicate a broad involvement in immune regulation, lipid metabolism, and cellular signaling, which are critical across various diseases.²⁷ The KEGG pathway analysis further highlights the engagement of these genes in pathways such as PI3K-Akt, TNF, JAK-STAT, and insulin signaling, which are implicated in inflammation, cell survival, and metabolic regulation, pointing to their relevance in cancer, autoimmune disorders, and cardiovascular diseases.

The hub genes play multifaceted roles in overall disease pathology. AKT1, a key regulator in the PI3K-Akt pathway, is essential for cell survival and proliferation, with dysregulation linked to cancers and neurodegenerative diseases.²⁸ STAT3, activated via the JAK-STAT pathway, drives inflammation and oncogenesis, making it a target in chronic inflammatory conditions and malignancies. ESR1, encoding the estrogen receptor, influences hormonal signaling and is implicated in breast cancer and metabolic syndromes.²⁹

TNF and IL6, cytokines central to immune responses, are elevated in autoimmune diseases and atherosclerosis, while NFKB1 regulates inflammation and apoptosis, contributing to cancer and inflammatory bowel disease.³⁰ EP300, a histone acetyltransferase, affects epigenetic regulation, linking it to developmental disorders and tumorigenesis.³¹ EGFR, involved in cell growth, is a therapeutic target in lung cancer, and BCL2, an anti-apoptotic protein, is critical in leukemia.³² APP, associated with Alzheimer's, reflects neuronal health, highlighting the diverse disease spectrum these genes influence.³³

Focusing on diabetes, these hub genes are intricately tied to its pathophysiology. AKT1 is a cornerstone in insulin signaling, promoting glucose uptake; its impairment leads to insulin resistance, a hallmark of Type 2 Diabetes (T2D).³⁴ STAT3 modulates pancreatic beta-cell function and insulin sensitivity, with overactivation exacerbating diabetic complications like neuropathy.³⁵ ESR1 influences adipose tissue distribution and insulin sensitivity, with estrogen deficiency linked to T2D risk in postmenopausal women.³⁶ TNF and IL6, elevated in obesity and T2D, drive chronic low-grade inflammation, contributing to insulin resistance and beta-cell dysfunction.³⁷ NFKB1 activation in diabetic vasculature promotes endothelial dysfunction, a precursor to cardiovascular complications. EP300 regulates gluconeogenesis, while EGFR and BCL2 affect beta-cell survival under oxidative stress, common in diabetes.³⁸ The overlapping targets (157) from phytochemical and diabetes-related genes, visualized in the PPI network (186 nodes, 259 edges), reinforce these connections, with the enriched pathways (e.g., insulin signaling, insulin resistance) underscoring their therapeutic relevance.

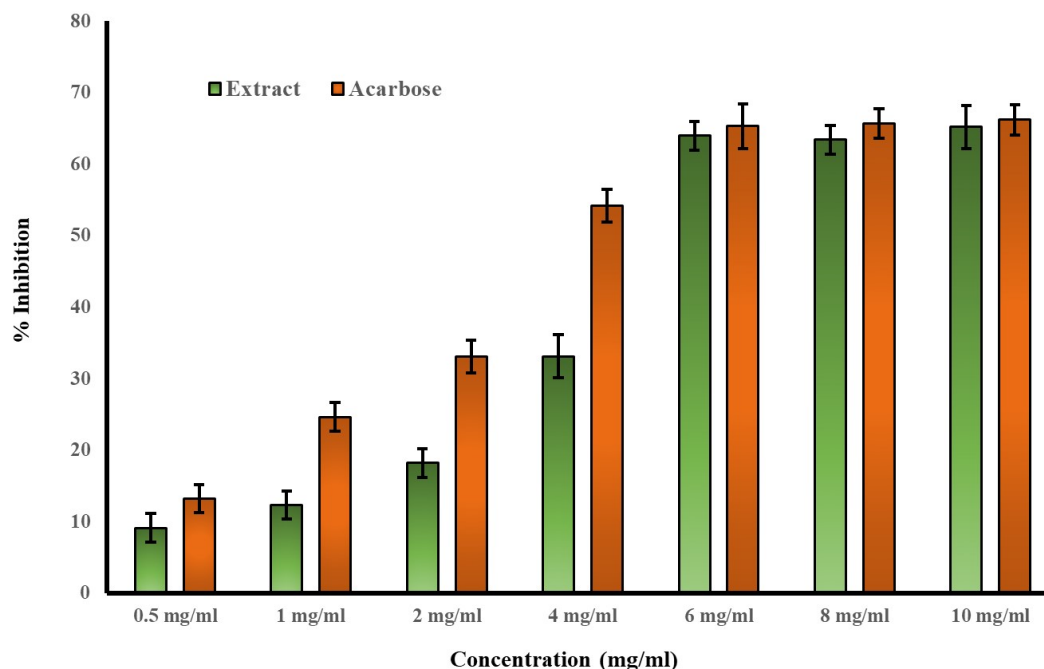


Figure 4A

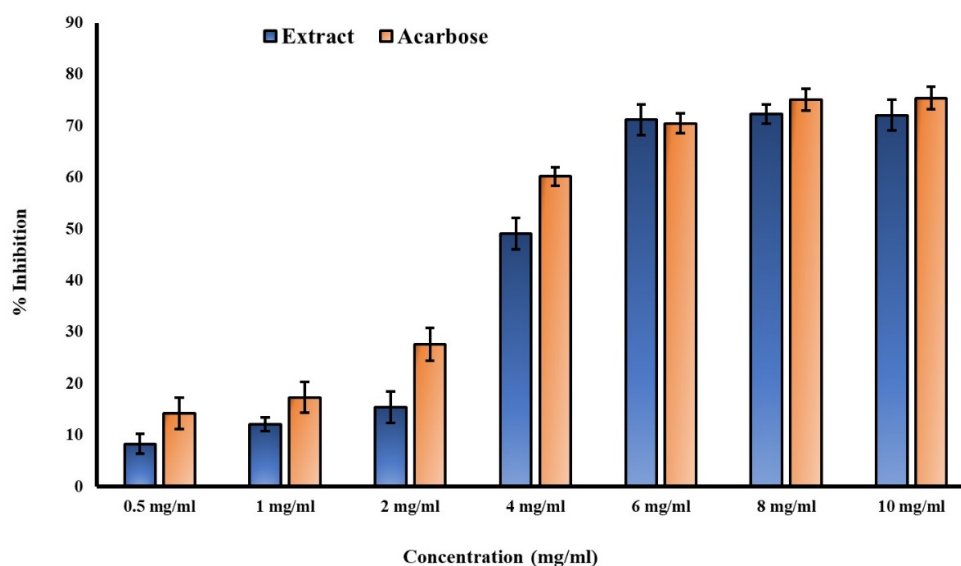


Figure 4B: (A) Effect of the *Curcuma longa* extract on the α -amylase inhibition at varying concentrations of the extract, results indicate a dose-dependent inhibition of α -amylase which was comparable with acarbose. (B) Effect of the *Curcuma longa* extract on the α -glucosidase inhibition at varying concentrations of the extract, results indicate a dose-dependent inhibition of α -amylase which was comparable with acarbose.

The molecular docking results, with Curcumin showing strong binding to STAT3 (-7.7 kcal/mol), AKT1 (-6.6 kcal/mol), and ESR1 (-6.7 kcal/mol), suggest a mechanism by which Curcumin from *Curcuma longa* (turmeric) could modulate these hub genes. Curcumin's interaction with STAT3 may reduce inflammation, a key diabetes driver, while its binding to AKT1 could enhance insulin sensitivity. The ESR1 interaction hints at metabolic regulation, aligning with *Curcuma longa*'s traditional use in managing metabolic disorders. The ADMET profiles of Curcumin and related compounds (Campesterol, Stigmasterol, Curcumenol, Curcumol, Procurcumadiol) indicate bioavailability and safety, supporting their potential as diabetes therapeutics. The plant-compound-target-pathway network ties *Curcuma longa*'s phytochemicals to these genes and pathways, positioning Curcumin as a promising agent to mitigate diabetic inflammation, insulin resistance, and vascular damage. This integrative approach highlights the therapeutic promise of *Curcuma longa* and Curcumin in diabetes management, leveraging their multi-target effects to address the disease's complex etiology.

The docking results of curcumin-STAT3 complex were further validated by MD simulation for stability, with the backbone RMSD stabilizing and ligand RMSD remaining low, reflecting a tightly bound pose. The sustained hydrogen bonds, alongside stable Radius of Gyration and Solvent Accessible Surface Area, reinforce the docking-predicted interactions, particularly with residues likely forming critical polar contacts. Minor RMSF peaks suggest localized flexibility, possibly in loop regions, without compromising overall integrity. Together, these findings confirm a strong Curcumin-STAT3 interaction, though extending the

simulation could provide deeper insights into long-term stability and dynamic behavior.

This study, while innovative, may be limited by its focus on a subset of phytochemicals, potentially overlooking minor compounds contributing to its antidiabetic effects of *Curcuma longa*, and the absence of *in vivo* validation, which is critical for confirming the extract's efficacy and safety in living organisms, thus restricting the translatability of the findings.

CONCLUSION

This study effectively showcases the antidiabetic potential of *Curcuma longa* extract using a combined approach of network pharmacology, *in vitro* assays, and molecular docking, identifying six key phytochemicals-Campesterol, Stigmasterol, Curcumenol, Curcumol, Curcumin, and Procurcumadiol-with favorable profiles, alongside 157 diabetes-related targets and hub genes (AKT1, ESR1, STAT3) linked to PI3K-Akt, TNE, and insulin signaling pathways. Molecular docking confirmed strong curcumin binding to STAT3, AKT1, and ESR1, reinforced by MD simulations showing a stable Curcumin-STAT3 complex with consistent RMSD, minimal ligand deviation, sustained hydrogen bonds, and stable Radius of Gyration and Solvent Accessible Surface Area over 10 ns. *In vitro* assays demonstrated significant α -amylase and α -glucosidase inhibition, matching acarbose's efficacy. However, limitations include the focus on a subset of phytochemicals and lack of *in vivo* validation, which may restrict translatability, suggesting the need for further studies to explore minor compounds and confirm safety and efficacy *in vivo*.

ABBREVIATIONS

T2DM: Type 2 Diabetes Mellitus; **TCMSP:** Traditional Chinese Medicine Systems Pharmacology; **ADMET:** Absorption, Distribution, Metabolism, Excretion, and Toxicity; **PPI:** Protein-Protein Interaction; **GO:** Gene Ontology; **KEGG:** Kyoto Encyclopedia of Genes and Genomes; **DAVID:** Database for Annotation, Visualization and Integrated Discovery; **STRING:** Search Tool for the Retrieval of Interacting Genes/Proteins; **MW:** Molecular Weight; **OB:** Oral Bioavailability; **DL:** Drug-Likeness; **TNF- α :** Tumor Necrosis Factor-Alpha; **IL-6:** Interleukin-6; **MCP-1:** Monocyte Chemoattractant Protein-1; **NF- κ B:** Nuclear Factor-kappa B; **pNPG:** p-Nitrophenyl- α -D-Glucopyranoside; **AKT1:** Protein Kinase B Alpha; **TCM:** Traditional Chinese Medicine; **MD:** Molecular Dynamics; **BP:** Biological Process; **CC:** Cellular Component; **MF:** Molecular Function; **FDR:** False Discovery Rate; **RMSD:** Root Mean Square Deviation; **Rg:** Radius of Gyration; **SASA:** Solvent Accessible Surface Area; **RMSF:** Root Mean Square Fluctuation; **GIS:** Gene Importance Score; **ESR1:** Estrogen Receptor 1; **STAT3:** Signal Transducer and Activator of Transcription 3; **DNS:** Dinitrosalicylic Acid; **HIF-1:** Hypoxia-inducible factor 1; **VEGF:** Vascular endothelial growth factor; **T2D:** Type 2 Diabetes.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

This study investigates the antidiabetic potential of *Curcuma longa* (turmeric) extract through a multi-faceted approach combining *in vitro* enzyme assays, network pharmacology, and *in silico* molecular docking. From 133 phytochemicals screened via the TCMSP database, 52 were evaluated for ADMET and toxicity using Protox-3.0, SuperPred, and SwissTargetPrediction, with six compounds-Campesterol, Stigmasterol, Curcumenol, Curcumol, Curcumin, and Procurcumadiol-selected for favorable pharmacokinetic profiles. Ethanol-based Soxhlet extraction of *Curcuma longa* rhizomes yielded a gummy extract for *in vitro* testing. A compound-target network, constructed using Cytoscape and validated by SuperPred and SwissTargetPrediction, identified 157 overlapping diabetes-related targets from GeneCards, forming a Protein-Protein Interaction (PPI) network with 186 nodes and 259 edges via STRING and CytoHubba. Key hub genes (AKT1, ESR1, STAT3) were pinpointed, and Gene Ontology (GO) and KEGG analyses revealed enriched pathways, including PI3K-Akt, TNF, and insulin signaling, critical for inflammation, metabolism, and cell survival. Molecular docking using CBDOCK2 demonstrated strong binding affinities of curcumin with STAT3 (-7.7 kcal/mol), AKT1 (-6.6 kcal/mol), and ESR1 (-6.7 kcal/mol). *In vitro* assays confirmed dose-dependent inhibition of α -amylase (up to 65.2%) and α -glucosidase (up to 72.1%), comparable to acarbose, indicating potent antidiabetic

activity. These findings highlight *Curcuma longa*'s therapeutic potential in managing type 2 diabetes mellitus by targeting key molecular pathways and inhibiting carbohydrate-metabolizing enzymes, supporting further preclinical exploration.

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