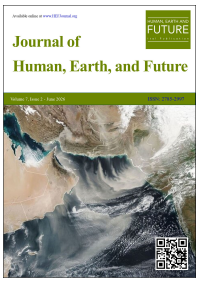
Available online at www.HEFJournal.org

ISSN: 2785-2997

Journal of
Human, Earth, and Future

Vol. 7, No. 2, June, 2026



Plant-Derived Multi-Target Modulators for Pre-Gestational Diabetes: Systems Insights into *Syzygium cumini* for Maternal Health

Putri Santy [1, 2], Amalia Sutriana [3*], Tongku Nizwan Siregar [4], Hamny Sofyan [5]

[1] *Graduate School of Mathematics and Applied Sciences, Universitas Syiah Kuala, Banda Aceh 23111, Indonesia.*

[2] *Department of Midwifery, Aceh Polytechnic of Health, Aceh Besar 23241, Indonesia.*

[3] *Laboratory of Pharmacology, Faculty of Veterinary Medicine, Universitas Syiah Kuala, Banda Aceh 23111, Indonesia.*

[4] *Laboratory of Reproduction, Faculty of Veterinary Medicine, Universitas Syiah Kuala, Banda Aceh 23111, Indonesia.*

[5] *Laboratory of Anatomy, Faculty of Veterinary Medicine, Universitas Syiah Kuala, Banda Aceh 23111, Indonesia.*

Received 16 July 2025; Revised 29 April 2026; Accepted 06 May 2026; Published 01 June 2026

Abstract

Pre-gestational diabetes (PGD), encompassing type 1 and type 2 diabetes diagnosed prior to conception, is a chronic metabolic disorder characterized by persistent hyperglycaemia, insulin resistance, impaired glucose uptake, and dysregulated lipid metabolism, posing substantial risks to maternal and fetal health. Given the multifactorial pathophysiology of PGD and limitations of single-target pharmacotherapy during pregnancy, this study aimed to elucidate the multi-target therapeutic potential of *Syzygium cumini* (*S. cumini*) bark phytoconstituents using an integrative network pharmacology and molecular docking approach. Comprehensive phytochemical profiling of the ethanolic bark extract was conducted using GC-MS and LC-HRMS, revealing fatty acids, sterol derivatives, and a flavonoid-dominant metabolite spectrum. Sixteen representative compounds were subjected to target prediction and mapped to PGD-related genes. The Protein–protein interaction analysis and functional enrichment (GO and KEGG) identified central regulatory nodes including PPAR-γ, glucose transporter (GLUT) proteins, and insulin receptor substrates associated with insulin signaling and metabolic homeostasis. Molecular docking against five PGD-relevant proteins (PDB IDs: 2PRG, 5EQI, 7WSN, 4F1D, 4ZW9) demonstrated strong binding affinities for flavonoids (quercetin, myricetin, kaempferol) and phytosterols (-8.1 to -10.4 kcal/mol), supporting the structural plausibility of multi-target interactions. Collectively, this study provides a systems-level mechanistic framework highlighting the potential of *S. cumini* as a complementary multi-pathway modulator in the management of pre-gestational diabetes.

Keywords: Pre-Gestational Diabetes; *S. cumini*; PPAR-γ; GLUT2; GLUT3; GLUT5; Insulin Resistance.

1. Introduction

Hyperglycemia in pregnancy (HIP) has emerged as a growing global public health challenge, reflecting the escalating burden of diabetes among women of reproductive age. According to the International Diabetes Federation (IDF), approximately 21.1 million live births in 2021 (16.7% of all births worldwide) were affected by some form of hyperglycaemia during pregnancy, with the majority attributed to gestational diabetes mellitus (GDM), while an estimated 6–7% of cases were due to pre-existing diabetes [1]. The World Health Organization (WHO) and the

* Corresponding author: amalia_sutriana@usk.ac.id

https://doi.org/10.28991/HEF-2026-07-02-011

International Federation of Gynecology and Obstetrics (FIGO) classify HIP into three major categories: pre-gestational diabetes (PGD), gestational diabetes mellitus (GDM), and diabetes in pregnancy (DIP). PGD refers to women with established type 1, type 2, or other forms of diabetes diagnosed prior to conception, whereas DIP denotes overt diabetes first identified during pregnancy that meets non-pregnant diagnostic thresholds, often detected early in gestation. Unlike GDM, which typically develops due to pregnancy-induced insulin resistance, PGD represents a chronic metabolic disorder preceding conception, thereby exposing both mother and fetus to prolonged hyperglycaemia before and throughout pregnancy. This sustained metabolic dysregulation significantly increases the risk of congenital malformations, preeclampsia, preterm delivery, macrosomia, and long-term cardiometabolic complications in offspring. Epidemiological trends indicate that the prevalence of PGD continues to rise in parallel with increasing obesity and type 2 diabetes rates among women of reproductive age, with global estimates suggesting that 1–2% of pregnancies are complicated by pre-existing diabetes, accompanied by substantial regional variability [2–4].

Given the multifactorial pathophysiology of PGD, plant-derived bioactive compounds have gained attention as potential complementary interventions due to their pleiotropic pharmacological properties. Among medicinal botanicals, *Syzygium cumini* L. (syn. *Eugenia jambolana* Lam.), commonly known as *jamblang* or Java plum, has attracted sustained scientific interest for its metabolic regulatory properties [5]. Phytochemical investigations consistently demonstrate that the bark contains a dense matrix of bioactive constituents, including gallic acid derivatives, ellagic acid, quercetin, kaempferol, catechins, tannins, alkaloids, saponins, and glycosides [6]. Notably, experimental validation has confirmed the presence of gallic acid, ellagic acid, and umbelliferone in bark decoctions and ready-to-serve herbal preparations, with these compounds individually reported to exhibit significant antidiabetic activity through mechanisms involving glycaemic modulation and antioxidant effects [7]. These findings reinforce the ethnopharmacological credibility of bark-derived formulations. Preclinical investigations further substantiate the therapeutic potential of bark extracts. In streptozotocin- and alloxan-induced diabetic rodent models, both aqueous and ethanolic bark extracts significantly reduced fasting blood glucose levels, improved insulin sensitivity indices, and attenuated oxidative stress biomarkers, with efficacy profiles comparable to standard antidiabetic agents such as glibenclamide and metformin [8]. Chronic administration has additionally demonstrated reductions in glycated hemoglobin (HbA1c), serum triglycerides, and low-density lipoprotein cholesterol, indicating broader metabolic improvement beyond glycaemic control [9]. Histopathological analyses have also reported partial restoration of pancreatic β-cell architecture and enhancement of endogenous antioxidant defense systems, including superoxide dismutase and catalase activity. Collectively, these mechanistic and experimental observations provide a compelling rationale for investigating *S. cumini* bark within a systems-based, multi-target framework relevant to the complex metabolic dysregulation characteristic of pre-gestational diabetes.

Mechanistic investigations attribute these antihyperglycemic effects to several interrelated pathways. Notably, *S. cumini* bark extract appears to facilitate regeneration of pancreatic β-cells and enhance endogenous insulin secretion [10]. Additional effects include improvement of peripheral insulin sensitivity and inhibition of α-glucosidase activity, thereby mitigating postprandial glycemic excursions [11]. Beyond glycemic modulation, *S. cumini* bark exhibits significant antihyperlipidemic activity. Experimental studies have reported improved lipid profiles characterized by reductions in total cholesterol, low-density lipoprotein (LDL), and triglycerides, accompanied by elevations in high-density lipoprotein (HDL) cholesterol levels [12, 13].

Recent investigations further reinforce these findings through integrative computational and experimental approaches. A network pharmacology analysis identified key regulatory pathways modulated by *S. cumini* phytoconstituents, including insulin signaling, PI3K-Akt pathway activation, and glucose transporter regulation, highlighting a multi-target mode of action rather than isolated enzyme inhibition [14]. Complementing this systems-level perspective, an integrative study combining network pharmacology with in vitro glucose uptake assays demonstrated that selected *S. cumini* phytochemicals significantly enhanced cellular glucose uptake while interacting with multiple metabolic hub proteins [15]. Although randomized clinical trials specific to pre-gestational diabetes remain limited, the convergence of classical pharmacological data and emerging systems-based analyses strengthens the translational plausibility of *S. cumini* bark as a complementary therapeutic candidate for PGD. Its multimodal mechanisms, encompassing glycemic regulation, lipid homeostasis, antioxidative defense, inflammatory modulation, and network-level metabolic control, warrant deeper mechanistic validation and carefully designed clinical investigations.

To address this gap, the present study integrates dual-platform metabolite profiling (GC-MS and LC-HRMS) with network pharmacology and molecular docking to elucidate the multi-target therapeutic potential of *S. cumini* bark in the context of PGD. By combining phytochemical characterization, target prediction, protein–protein interaction network analysis, enrichment interpretation, and structural binding validation, we aim to move beyond descriptive phytochemistry toward a systems-level mechanistic understanding. This integrative framework enables identification of key regulatory nodes and pathways potentially modulated by bark-derived phytoconstituents, thereby providing a rational basis for exploring *S. cumini* as a complementary strategy for managing the complex metabolic disturbances

associated with pre-gestational diabetes. By integrating molecular docking studies, this study seeks to validate key compound-target interactions involved in insulin signaling, glucose transport, and lipid homeostasis, thereby bridging empirical knowledge with mechanistic insights. Such an approach will not only elucidate the pharmacological nature of *S. cumini* but also provide a scientific foundation for its clinical application in PGD management. Ultimately, this research strives to contribute to evidence-based, integrative strategies for improving maternal-fetal health outcomes in diabetic pregnancies.

2. Material and Methods

2.1. Study Design

To systematically elucidate the molecular mechanisms underlying the antidiabetic potential of *S. cumini* bark, an integrated workflow was established (Figure 1). Initially, comprehensive phytochemical profiling was conducted using GC–MS and LC–HRMS to characterize the chemical diversity of the ethanolic extract. Selected bioactive compounds were subsequently subjected to target prediction using SwissTargetPrediction, enabling identification of potential protein targets based on structural similarity principles. Disease-associated genes related to pre-gestational diabetes were retrieved from GeneCards and OMIM databases and intersected with predicted compound targets to identify shared molecular nodes. These overlapping targets were analyzed using the STRING database to construct a protein–protein interaction (PPI) network and determine key regulatory hubs. Finally, molecular docking analysis was performed to validate the binding interactions between prioritized phytoconstituents and selected PGD-related protein targets. This integrative systems-pharmacology framework enables mechanistic interpretation beyond single-target analysis and supports a multi-pathway therapeutic perspective.

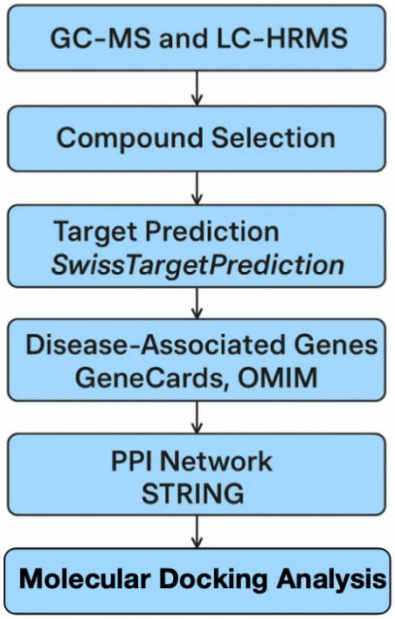


Figure 1. Integrated workflow of phytochemical profiling and systems pharmacology analysis.

2.2. Plant Collection and Extraction Process

Fresh bark of *S. cumini* was harvested from cultivated land in Aceh Province, Indonesia, and authenticated by a taxonomist at the Herbarium of Universitas Syiah Kuala (No. 458/UN11.1.8.4/TA.00.03/2024). The bark was thoroughly rinsed, shade-dried to preserve thermolabile phytoconstituents, and ground into coarse powder. A total of 500 g of dried powder was macerated in 96% ethanol for 72 hours at ambient temperature with periodic agitation to enhance extraction efficiency. Ethanol was selected as the extraction solvent due to its intermediate polarity, which enables efficient recovery of a broad spectrum of phytochemicals, including flavonoids, phenolic acids, tannins, sterols, and certain lipid derivatives. Compared to highly polar solvents such as water or less polar solvents such as hexane, ethanol provides a balanced extraction profile suitable for capturing chemically diverse metabolites relevant to metabolic regulation. Additionally, ethanol is pharmaceutically acceptable, relatively safe, and fully compatible with downstream GC–MS and LC–HRMS analyses. Consistent with prior reports, our findings highlight that solvent polarity plays a critical role in phytochemical extraction, with ethanol yielding the most chemically diverse profile of bioactive compounds detected in the extract. This observation provides a strategic framework for solvent selection in future phytochemical and pharmacological investigations, depending on the targeted compound class [16]. The extract was subsequently filtered and concentrated under reduced pressure using a rotary evaporator at 40°C to minimize thermal degradation. The concentrated crude extract was stored at 4°C until further analysis.

2.3. Phytochemical Profiling Using Gas Chromatography-Mass Spectroscopy (GC-MS)

The chemical constituents of the ethanolic extract were profiled using Gas Chromatography–Mass Spectrometry (TRACE 1310 GC coupled with a single quadrupole iSQ 7000, Thermo Fisher Scientific, USA) equipped with a TraceGOLD TG-35MS column (30 m × 0.25 mm × 0.25 µm). Helium was used as the carrier gas at a constant flow rate of 1 mL/min. The injector and ion source temperatures were maintained at 250°C. The oven temperature was programmed from 60°C to 280°C at a rate of 10°C/min. A fixed injection volume of the extract was introduced in split mode. Compound identification was based on retention time and mass spectral matching against NIST and Wiley spectral libraries. Only peaks with a spectral match quality ≥85% were considered for tentative identification. To ensure analytical reliability, solvent blanks were injected under identical conditions to monitor background signals and potential contamination. Peaks present in blank runs were excluded from compound assignment [17].

2.4. Phytochemical Profiling Using Liquid Chromatography-High Resolution Mass Spectroscopy (LC-HRMS)

To comprehensively characterize the secondary metabolites, present in the ethanolic extract of *S. cumini*, liquid chromatography coupled with high-resolution mass spectrometry (LC–HRMS) analysis was performed. This technique enables high-resolution separation and accurate mass detection of chemically diverse constituents within complex botanical matrices. Chromatographic separation was carried out using a reverse-phase C18 column with a gradient mobile phase consisting of water (0.1% formic acid) and acetonitrile. Samples were analyzed under both positive and negative electrospray ionization modes to maximize metabolite coverage. Metabolite identification was performed through accurate mass measurement (m/z), isotopic pattern evaluation, and MS/MS fragmentation pattern comparison against established spectral libraries and databases. Compound annotation confidence was assigned according to the Metabolomics Standards Initiative (MSI) guidelines. Metabolites matched based on accurate mass and fragmentation pattern without confirmation using authentic reference standards were classified as Level 2 (putatively annotated compounds). Compounds identified based solely on accurate mass without diagnostic MS/MS confirmation were designated as Level 3 (putatively characterized compound classes). No Level 1 confirmation (reference standard co-elution and spectral matching) was performed in this study. Through this approach, a diverse metabolite spectrum was annotated, including flavonoids, phenolic acids, carboxylic acid derivatives, and steroidal compounds. These annotated metabolites provide insight into the chemical complexity of the extract and form the basis for subsequent network pharmacology and molecular docking analyses [18].

2.5. Network Pharmacology Analysis

Network pharmacology was employed to explore the potential multi-target mechanisms of *S. cumini* in managing pre-gestational diabetes. Bioactive compounds were selected based on prior phytochemical profiling using GC-MS and LC-HRMS of the plant extract. Only structurally identified compounds with relevant biological plausibility were included in the analysis. Target prediction for each compound was performed using SwissTargetPrediction (http://www.swisstargetprediction.ch/), restricted to *Homo sapiens* [19]. Disease-associated genes related to pre-gestational diabetes and type 2 diabetes mellitus were retrieved from the GeneCards and Online Mendelian Inheritance in Man (OMIM) databases using the keywords “pre-gestational diabetes” and “type 2 diabetes mellitus". To reduce false-positive associations and improve target specificity, only genes with a GeneCards relevance score higher than the mean score of all retrieved entries were retained for subsequent analysis. OMIM-listed genes were included as high-confidence disease-associated targets. Duplicate entries were removed prior to downstream network construction [20, 21]. The overlapping targets between predicted compound targets and diabetes-related genes were identified manually and used to construct the basis for protein–protein interaction (PPI) analysis. The PPI network was generated using the STRING database (Version 11.5, *https://string-db.org*), with a minimum required interaction score of 0.7 (high confidence) and the organism set to *H. sapiens* [22]. The resulting networks and enriched pathways were interpreted to uncover the pharmacological landscape of *S. cumini* in targeting the multifactorial aspects of pre-gestational diabetes.

2.6. Molecular Docking Analysis

A molecular docking analysis was conducted to evaluate the binding potential of sixteen representative bioactive compounds identified from the GC–MS and LC–HRMS profiling of the ethanolic extract of *S. cumini* bark. Compound selection was performed using predefined criteria to ensure analytical reliability and biological relevance. Specifically, compounds were included if they met the following conditions: (i) high-confidence spectral annotation based on library matching (GC–MS match quality ≥ threshold; LC–HRMS putative identification with consistent m/z and fragmentation pattern), (ii) relative abundance within the extract, indicating meaningful phytochemical representation, (iii) documented or plausible relevance to metabolic regulation based on literature evidence, and (iv) availability of validated three-dimensional structural data for docking preparation. Compounds suspected to arise from derivatization artifacts or lacking structural confirmation were excluded from docking analysis. The identified compounds from the GC-MS and LC-HRMS analysis were cross-checked with the PubChem database to obtain their 2D and 3D chemical structures [19]. These structures were converted into appropriate file formats using Open Babel and subsequently

energy-minimized using the MMFF94 force field. The ligands were prepared in PDBQT format using AutoDock Tools, ensuring proper protonation and removal of any redundant structures. The three-dimensional structure of the PPAR-γ, GLUT transporters, and insulin receptor domain was obtained from the RCSB Protein Data Bank (Table 1). Non-essential molecules such as crystallographic water, ions, and co-crystallized ligands were removed. Polar hydrogens were added, and Gasteiger charges were assigned. The refined protein structure was minimized and saved in PDBQT format for docking purposes. Molecular docking was performed using AutoDock Vina to evaluate the binding affinities of *S. cumini*-derived compounds toward PGD-related receptors. The active site was defined based on literature and ligand-binding site information. A grid box encompassing the active site was constructed with sufficient dimensions to accommodate various ligand conformations. Each ligand was docked individually, and the binding affinities were recorded in kcal/mol. Post-docking analyses, including hydrogen bonding and hydrophobic interaction mapping, were carried out using Discovery Studio Visualizer. In this study, metformin was used as the positive control to benchmark the potential antidiabetic effects of *S. cumini* phytoconstituents. Compounds demonstrating strong binding affinities (kcal/mol) and favorable interactions with critical residues of the insulin receptor were shortlisted [23].

Table 1. Receptors of molecular docking study

Descriptions	PDB ID
Human insulin	4F1D
Human GLUT1	5EQI
Human GLUT3	4ZW9
Human GLUT4	7WSN
Human Peroxisome Proliferator Activated Receptor Gamma	2PRG

3. Results and Discussion

Phytocompounds from the ethanolic extract of *S. cumini* were identified using GC-MS and LC-HRMS. The GC-MS is a powerful analytical technique that enables the separation, identification, and quantification of volatile and semi-volatile compounds based on their unique mass-to-charge (m/z) ratios and retention times. In this study, the GC-MS analysis produced characteristic spectral patterns that were matched against established library databases (e.g., NIST), resulting in the identification of several major phytoconstituents. These included *n*-hexadecanoic acid, fatty acid methyl esters, sterol derivatives, and fatty acid hydrazides, all of which are known to possess various biological activities, including antioxidant, anti-inflammatory, and metabolic regulatory effects (Table 2).

In parallel, LC-HRMS analysis was conducted to characterize the non-volatile and thermally labile secondary metabolites present in the extract with high mass accuracy and sensitivity. This method enabled the detection of a broader range of phytochemicals, particularly polar and high-molecular-weight compounds that are not amenable to GC-MS. The LC-HRMS profiling revealed a rich diversity of bioactive constituents, notably from the flavonoid, carboxylic acid, and steroidal classes, which are frequently associated with antidiabetic and cardioprotective properties. Together, the complementary use of GC-MS and LC-HRMS provided a comprehensive phytochemical profile of *S. cumini*, forming the basis for subsequent bioinformatics and pharmacological analyses.

Table 2. Phytocompounds from ethanolic extract of *S. cumini*

No.	Compound Name	Similarity Index (%)	PubChem ID
1	*n*-Hexadecanoic acid (Palmitic acid)	97.67	985
2	Hexadecanoic acid, methyl ester	92.04	8181
3	Methyl (Z)-10-pentadecenoate	94.28	13833982
4	Stigmasta-3,5-diene	97.12	13783149
5	Stigmastan-3-ol, 5-chloro-, acetate, (3ß,5a)-	97.11	22216978
6	16-Hexadecanoyl hydrazide	96.72	225536
7	Myristic acid glycidyl ester	87.18	346148
8	9,9-Dimethoxybicyclo[3.3.1]nona-2,4-dione	92.11	537288
9	(R)-(-)-4-Methylhexanoic acid	82.83	12600623
10	1,5,9,9-Tetramethyl-2-oxatricyclo[6.4.0.0(4,8)]dodecane	83.17	586811
11	Androstane-11,17-dione, 3-[(trimethylsilyl)oxy]-, 17-[O-(phenylmethyl)oxime]	92.67	20845500
12	Z-10-Tetradecen-1-ol acetate	98.70	5363221
13	Ergosta-5,22-dien-3-ol, acetate, (3ß,22E)-	95.55	13889457

Metabolite profiling of the ethanolic extract of *S. cumini* bark via LC-HRMS revealed a diverse range of bioactive compounds, which were classified into several key chemical subclasses. Among them, flavonoids, carboxylic acids and their derivatives, and steroidal compounds were particularly prominent, each contributing to the extract's potential pharmacological effects (Figure 2). The flavonoid group was the most represented subclass, consisting of four well-known polyphenolic antioxidants: myricetin, epigallocatechin gallate, quercetin, and kaempferol. These compounds are known for their strong radical-scavenging activities and modulatory effects on glucose metabolism and insulin sensitivity. Flavonoids also exhibit anti-inflammatory and vasoprotective properties, which are particularly relevant in the context of gestational diabetes, where oxidative stress and endothelial dysfunction play key roles [24, 25].

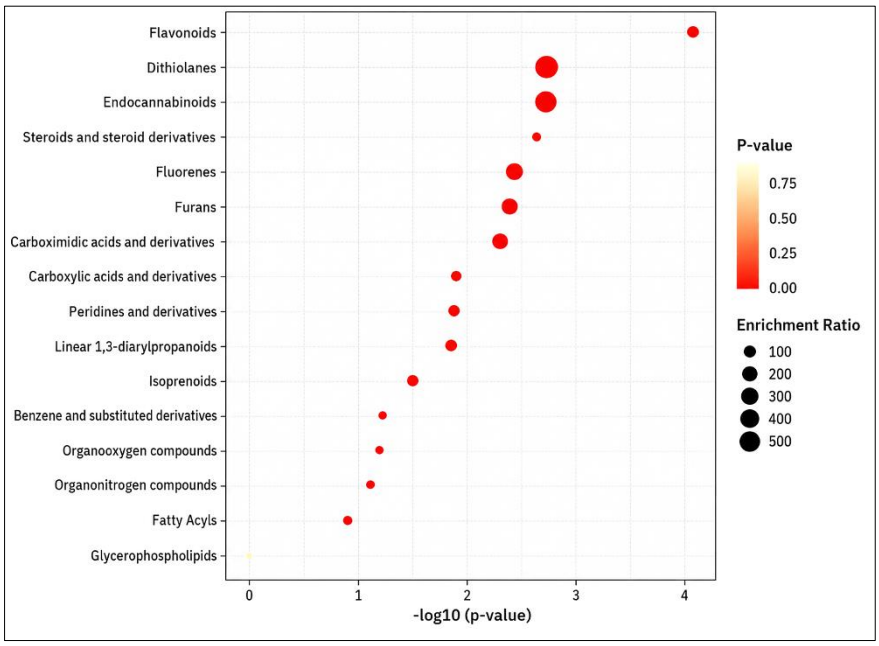


Figure 2. Overview of bioactive compound from *S. cumini* extract based on LC-HRMS analysis.

The present study is grounded in a systems-pharmacology framework, recognizing pre-gestational diabetes (PGD) as a multifactorial metabolic disorder driven by interconnected molecular networks rather than a single pathogenic node. PGD involves chronic insulin resistance, impaired glucose transport, dysregulated lipid metabolism, oxidative stress, and inflammatory signaling that collectively disrupt metabolic homeostasis. Such network-based dysregulation suggests that therapeutic strategies targeting a single enzyme or receptor may be insufficient to restore systemic balance. Therefore, a multi-target paradigm is theoretically more appropriate for addressing PGD pathophysiology. Network pharmacology provides a computational strategy to model interactions between multiple bioactive compounds and disease-associated molecular networks [18]. Unlike reductionist approaches that evaluate isolated compound–target pairs, this methodology enables identification of shared regulatory hubs, central nodes, and enriched pathways within protein–protein interaction networks. In PGD, a deeper understanding of glucose transport and insulin signaling pathways is pivotal. Network pharmacology studies targeting key proteins, namely insulin, glucose transporters (GLUT1, GLUT3, GLUT4), and peroxisome proliferator-activated receptor gamma (PPAR-γ), can provide mechanistic insights into how phytoconstituents such as those found in *S. cumini* bark exert antihyperglycemic effects (Figure 3). GLUT1 and GLUT3 play vital roles in basal and placental glucose transport [26].

The alterations in their expression disrupt maternal-fetal glucose exchange. Previous study showed the increased of GLUT1 mRNA in placentas from diabetic pregnancies, yet GLUT3 expression may be variably affected, particularly in insulin-dependent states [27]. Moreover, sex hormone binding globulin (SHBG) expression has been shown to influence GLUT1, GLUT3, and GLUT4 expression in insulin-resistant cells, further linking hormonal regulation to transporter availability [28]. GLUT4 is the principal insulin-responsive glucose transporter in adipose and muscle tissues. In PGD, there is a noted defect in GLUT4 translocation and subcellular distribution, not just in quantity. Half of the patients with PGD may exhibit profound GLUT4 depletion, while all show impaired GLUT4 translocation despite preserved insulin signaling upstream [29]. Additionally, impaired GLUT4 gene regulation through inflammatory and metabolic pathways in PGD may reduce insulin responsiveness [30]. PPAR-γ is a master regulator of adipogenesis, insulin sensitivity, and glucose metabolism. It modulates the expression of both GLUT1 and GLUT4. The downregulation of PPAR-γ may contribute to insulin resistance. In vitro and in vivo models show that PPAR-γ agonists, including natural ligands and thiazolidinediones, enhance GLUT4 translocation and insulin responsiveness in adipocytes [31].

Network pharmacology integrates systems biology and computational modelling to map the complex interactions between drugs, targets, and diseases. Key network metrics such as degree, betweenness centrality, and closeness centrality can help identify essential nodes (proteins or genes) that may serve as critical therapeutic targets [32]. In this

study, we analyzed the topological properties of five key proteins: insulin (INS), GLUT1, GLUT3, GLUT4, and PPAR-γ, with the aim of identifying their relative importance within a biological interaction network relevant to glucose transport and insulin signaling (Figure 3).

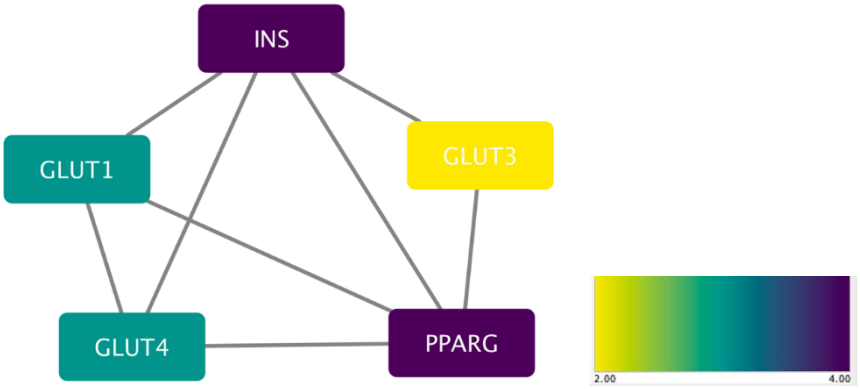


Figure 3. Topological network of five key target receptors

Insulin, or INS, displays the highest values across all three centrality measures (degree = 4, betweenness = 0.167, closeness = 1.0), indicating its role as a central hub in the network (Table 3). This aligns with insulin's established function as a key regulator of glucose homeostasis, modulating the translocation of glucose transporters such as GLUT4 to the plasma membrane in muscle and adipose tissues [33, 34]. GLUT4 is well-known as the insulin-responsive glucose transporter, and its degree (3) and closeness (0.8) reflect this intermediate position. Though not a hub like INS, its critical role in insulin-mediated glucose uptake supports its functional importance [31]. GLUT1, a ubiquitous and constitutive glucose transporter, shares similar metrics with GLUT4 (degree = 3, closeness = 0.8), indicating a comparable network role. Its broad expression supports basal glucose uptake across cell types [35]. Despite its importance, the lack of betweenness centrality suggests it operates independently of major information flow, consistent with its constitutive function. GLUT3 has the lowest degree and closeness centrality, indicating a more peripheral role in the network. GLUT3 is primarily expressed in neurons and is specialized for high-affinity glucose uptake [36]. Its lower connectivity reflects its tissue-specific function rather than lack of importance, emphasizing the context-dependent role of centrality metrics. The network analysis highlights INS and PPAR-γ as key hub proteins with central roles in metabolic regulation and potential drugability. GLUT4 and GLUT1 are important but play more targeted roles downstream of insulin signaling. GLUT3, while critical in neurons, appears functionally specialized and less central in a broader metabolic context. This analysis underscores the utility of network metrics in uncovering hidden regulatory roles and prioritizing proteins for further study in drug development and systems pharmacology.

Table 3. Network Centrality Measures of Selected Proteins

Protein	Degree	Betweenness Centrality	Closeness Centrality
INS	4	0.167	1.000
PPARG	4	0.167	1.000
GLUT4	3	0.000	0.800
GLUT1	3	0.000	0.800
GLUT3	2	0.000	0.667

Molecular docking further complements this theoretical framework by providing structural validation of predicted compound–target interactions. While network analysis identifies topological importance within biological systems, docking assesses binding plausibility at the atomic level, thereby bridging systems biology with structural pharmacology. The convergence of network centrality and strong binding affinity observed for flavonoids and phytosterols reinforces the hypothesis that *S. cumini* phytoconstituents act through cooperative multi-target mechanisms rather than isolated receptor modulation. A molecular docking analysis was conducted to evaluate the binding potential of 16 bioactive compounds identified from the GC-MS and LC-HRMS profiling of ethanolic extract *S. cumini*. These compounds were docked against five protein targets (PDB IDs: 4F1D, 4ZW9, 2PRG, 5EQI, and 7WSN), which are associated with key mechanisms involved in insulin signaling, glucose metabolism, and lipid regulation—pathways central to the pathophysiology of pre-gestational diabetes. The compounds included a variety of chemical classes, reflecting the chemical diversity of the *S. cumini* extract. From the GC-MS analysis, several fatty acids and lipid derivatives were identified: *n*-hexadecanoic acid, hexadecanoic acid methyl ester, methyl (Z)-10-pentadecenoate, myristic acid glycidyl ester, (R)-(-)-4-methylhexanoic acid, and Z-10-tetradecen-1-ol acetate. These

molecules are known for their metabolic regulatory and anti-inflammatory properties. Additionally, sterol and steroid-related compounds such as stigmasta-3,5-diene, stigmastan-3-ol, 5-chloro-, acetate (3β,5α), and ergosta-5,22-dien-3-ol acetate (3β,22E) were included, representing the phytosterol content of the extract, which is often linked to lipid-lowering and insulin-sensitizing effects. The extract also contained more structurally unique compounds, including 16-hexadecanoyl hydrazide, a fatty acid hydrazide; 9,9-dimethoxybicyclo[3.3.1]nona-2,4-dione, a tricyclic ether-ketone; and 1,5,9,9-tetramethyl-2-oxatricyclo[6.4.0.0(4,8)]dodecane, a compact oxygenated tricyclic compound. Although less commonly studied, such structures may offer novel bioactivity through enzyme modulation or receptor interactions. In parallel, LC-HRMS analysis revealed the presence of prominent flavonoid constituents, namely gallic acid, myricetin, quercetin, and kaempferol—compounds with well-documented antioxidant, anti-inflammatory, and antidiabetic activities. These flavonoids are known to influence key targets such as PPAR-γ, GLUT transporters, and insulin receptor substrates, making them valuable candidates for molecular docking.

The docking results were visualized using a heatmap (Figure 4), providing a comparative overview of the binding affinities of all 16 compounds across the five protein targets. The receptor targets chosen for this study are all associated with key processes in carbohydrate and lipid metabolism. For instance, 4F1D is the catalytic domain of human maltase-glucoamylase, a validated target in type 2 diabetes due to its role in carbohydrate digestion [37]. 2PRG represents PPAR-γ, a nuclear receptor central to lipid metabolism and insulin sensitization, and a target of thiazolidinedione drugs [38]. The remaining targets, including 5EQI and 7WSN, are likely involved in glucose transport or metabolism, further supporting the relevance of the observed binding patterns. This analysis offered critical insights into the multi-target binding capabilities of *S. cumini* phytoconstituents and highlighted several compounds, particularly flavonoids and sterols, as having strong binding interactions with key metabolic regulators.

Among the screened compounds, ergosta-5,22-dien-3-ol acetate exhibited the strongest and most consistent binding affinities across all receptor proteins, with docking scores ranging from -8.1 to -10.4 kcal/mol (Figure 4). This phytosterol derivative, commonly found in fungi and some medicinal plants, has been previously associated with anti-inflammatory, anticancer, and antidiabetic properties, possibly due to its structural similarity to cholesterol and ability to modulate nuclear receptor activity [39]. Similarly, stigmasta-3,5-diene and stigmastan-3-ol, 5-chloro-, acetate also demonstrated strong binding, especially to 5EQI and 7WSN, which are likely involved in glucose metabolism based on protein homology. The flavonoids quercetin, myricetin, and kaempferol consistently showed moderate to strong docking scores across all targets. These polyphenolic compounds are well known for their antioxidant, anti-inflammatory, and metabolic regulatory properties [24]. Their ability to modulate insulin secretion, improve glucose uptake, and interact with metabolic enzymes and nuclear receptors such as PPAR-γ has been well documented [40]. In particular, quercetin has been shown to inhibit sodium-glucose transporters (e.g., SGLT1, GLUT2), and its observed high affinity in this study for the 7WSN receptor may reflect a similar mechanism of action. Fatty acids and their methyl esters, such as *n*-hexadecanoic acid and methyl (Z)-10-pentadecenoate, exhibited relatively weaker binding, with docking scores clustering around -5 to -6 kcal/mol. While these compounds are known to modulate metabolic pathways indirectly such as influencing membrane fluidity, signaling cascades, and PPAR activation, they did not show high direct binding affinity to the receptor targets in this docking context [41]. Nonetheless, their inclusion provides useful baseline comparisons for more potent phytochemicals.

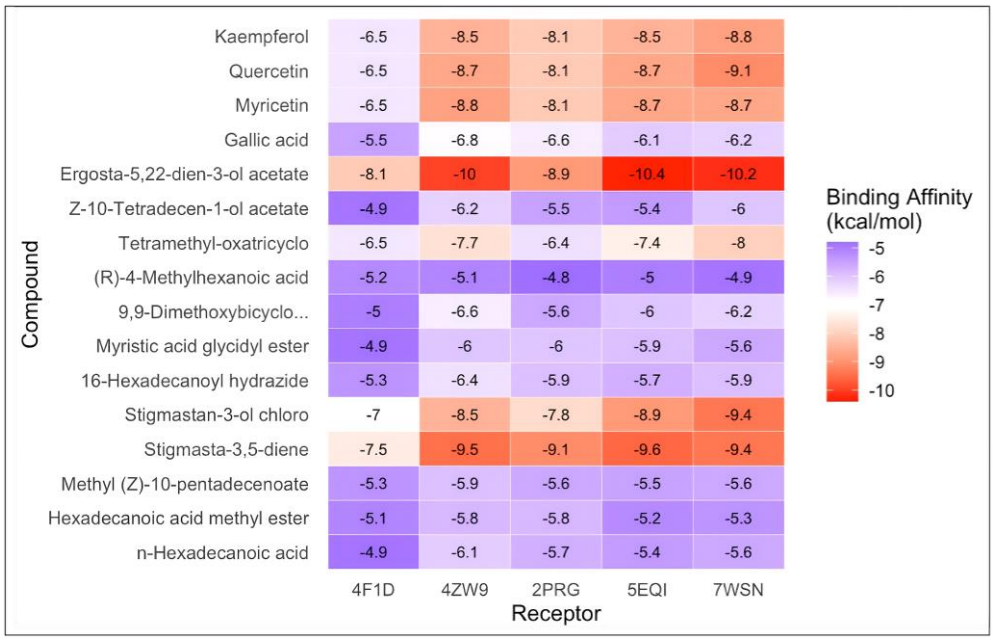
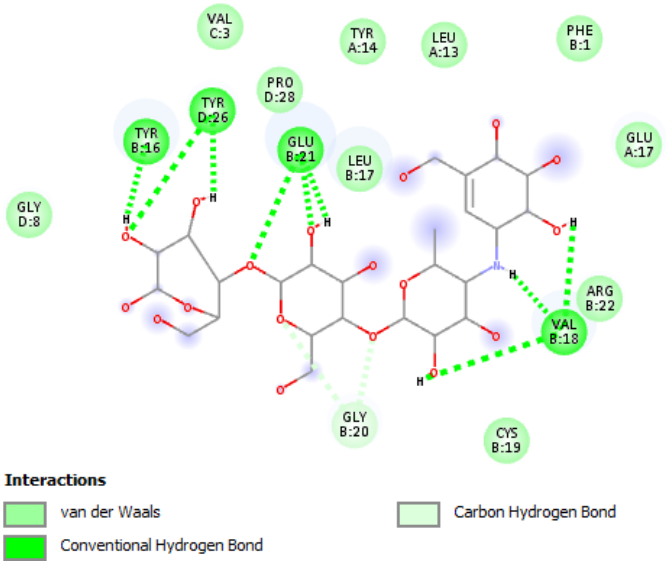


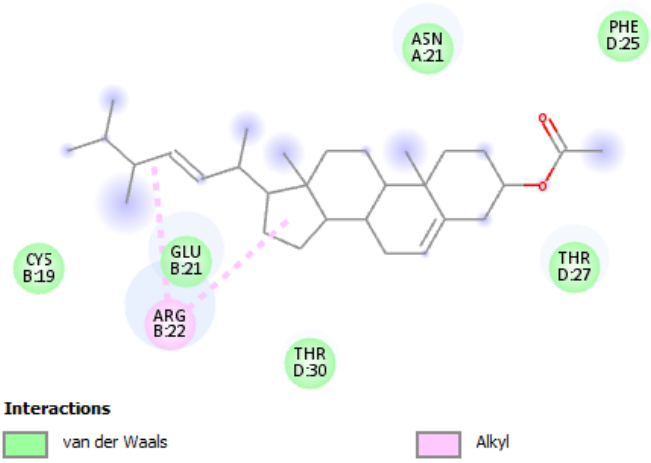
Figure 4. Docking score of active compounds from ethanolic extract of *S. cumini*

This study highlights a range of promising bioactive compounds with potential therapeutic relevance for metabolic disorders. Notably, several phytosterols, stigmasta-3,5-diene, stigmastan-3-ol, 5-chloro-, acetate (3β,5α), and ergosta-5,22-dien-3-ol, acetate (3β,22E), demonstrate structural features consistent with cholesterol-lowering and anti-inflammatory activity, making them attractive candidates for further investigation. In addition, the presence of potent flavonoids such as gallic acid, myricetin, quercetin, and kaempferol reinforces the therapeutic potential of the studied compounds. These flavonoids are well-documented for their antioxidant, enzyme-inhibitory, and insulin-sensitizing effects, which are crucial in addressing key pathways in metabolic disorders, including diabetes and obesity. Together, these phytochemicals offer a foundation for further exploration as multi-target modulators, supporting the development of integrated, plant-based strategies for the prevention and management of metabolic syndromes. The strong binding affinities of ergosta-5,22-dien-3-ol, acetate and stigmasta-3,5-diene, along with the consistent performance of flavonoids like quercetin, provide a compelling case for their potential utility in diabetes and obesity-related therapeutic development.

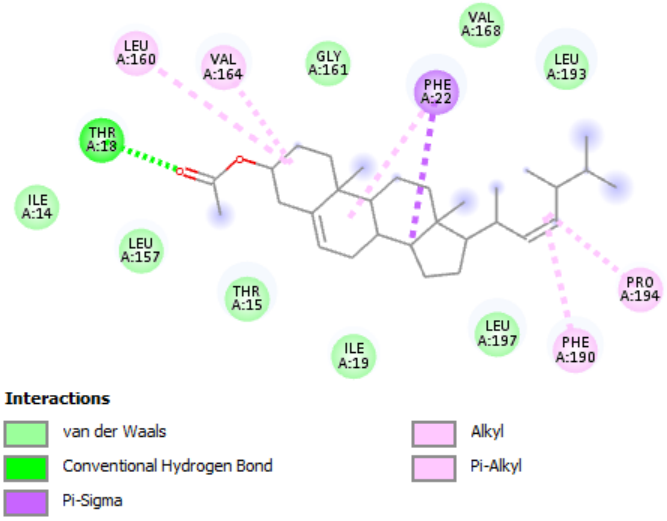
Visualization of ergosta-5,22-dien-3-ol, acetate, (3ß,22E) with receptors used in this study are presented in Figure 5. The interaction analysis revealed that ergosta-5,22-dien-3-ol, acetate, (3β,22E)- binds predominantly within hydrophobic pockets of the receptor proteins. Its steroidal backbone and acetyl group favor non-polar interactions, while the hydroxyl group at position C3 potentially forms hydrogen bonds with polar amino acid residues. Hydrophobic interactions dominated the docking poses, particularly with residues such as Leu, Val, Ile, Phe, and Ala, which are frequently found within the binding sites of human insulin (4F1D) and human GLUT3 (4ZW9). Hydrogen bonding was observed in complexes with PPARγ (2PRG) and human GLUT1 (5EQI), where the hydroxyl moiety may engage with Ser, Thr, or Tyr residues, contributing to ligand stabilization. In the human GLUT4 (7WSN) complex, both hydrophobic and van der Waals interactions appeared significant, supporting the strong binding energy (-10.2 kcal/mol). These results suggest that ergosta-5,22-dien-3-ol, acetate can effectively interact with multiple targets involved in insulin signaling and inflammation, potentially modulating key pathways implicated in pre-gestational diabetes. The multi-target binding profile aligns with the principles of network pharmacology and supports its therapeutic relevance.



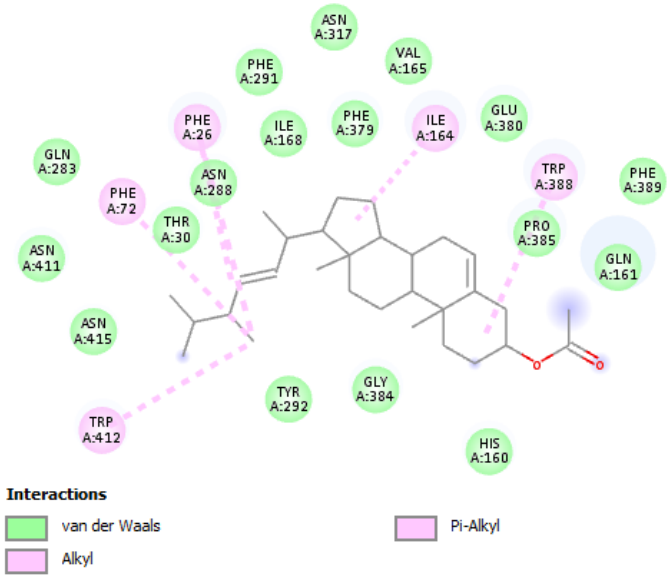
(a) Positive control (metformin) with human insulin



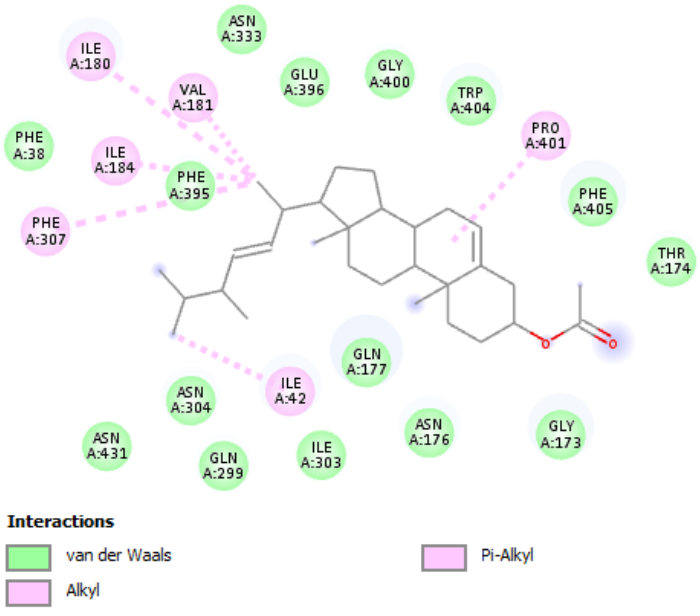
(b) Ergosta-5,22-dien-3-ol, acetate, (3ß,22E) with human insulin



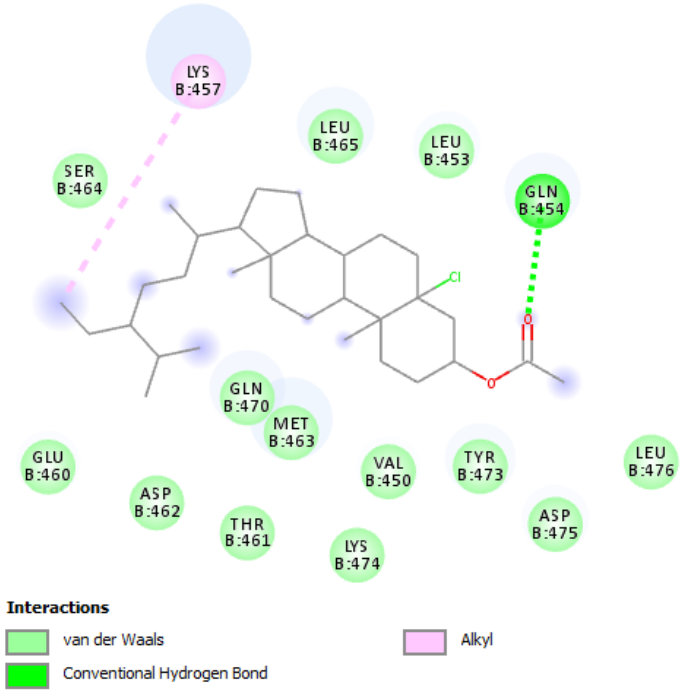
(c) Ergosta-5,22-dien-3-ol, acetate, (3ß,22E) with human GLUT3



(d) Ergosta-5,22-dien-3-ol, acetate, (3ß,22E) with human GLUT1



(e) Ergosta-5,22-dien-3-ol, acetate, (3ß,22E) with human GLUT4



(f) Ergosta-5,22-dien-3-ol, acetate, (3ß,22E) with PPARRG

Figure 5. Visualization of ergosta-5,22-dien-3-ol, acetate, (3ß,22E) and the receptors

The interaction of *S. cumini* bark phytocompounds with key metabolic receptors, namely the insulin receptor, GLUT1, GLUT3, GLUT4, and PPAR-γ, provides a compelling mechanistic rationale for its potential antihyperglycemic effects in the PGD. These molecular targets play central roles in maintaining glucose homeostasis and are closely interlinked in both systemic and pregnancy-specific metabolic regulation. Activation of the insulin receptor initiates a signaling cascade that leads to the translocation of GLUT4 to the cell membrane, facilitating glucose uptake in insulin-responsive tissues such as muscle and adipose. Meanwhile, PPAR-γ serves as a nuclear receptor that not only enhances insulin sensitivity but also upregulates the transcription of GLUT genes, further promoting glucose uptake. Importantly, GLUT1 and GLUT3 are highly expressed in the placenta and are critical for ensuring an adequate maternal-fetal glucose supply. Dysregulation of these transporters is commonly observed in PGD, contributing to fetal overgrowth and metabolic complications. The findings from this study suggest that flavonoids and phytosterols from *S. cumini* may exert multi-target regulatory effects by modulating this glucose transport and signaling axis. Molecular docking results revealed strong binding affinities between selected phytocompounds, such as quercetin, myricetin, kaempferol, and ergosta-5,22-dien-3-ol acetate, and the aforementioned protein targets, supporting the hypothesis of their therapeutic potential in mitigating insulin resistance and restoring glucose balance in PGD.

Experimental and clinical investigations consistently support the antidiabetic potential of *S. cumini*. In an alloxan-induced diabetic rat model, administration of polyphenolic-rich extracts of *S. cumini* leaves significantly reduced fasting blood glucose, glycated hemoglobin (HbA1c), insulin resistance indices (HOMA-IR), lipid peroxidation levels, and glucose-6-phosphatase activity, while enhancing glycogen storage, insulin secretion, pancreatic β-cell integrity, antioxidant enzyme activity, hexokinase function, and glucose transporter expression ($P < 0.05$) [42]. These findings indicate not only antihyperglycemic activity but also anti-inflammatory and antioxidative effects, suggesting restoration of metabolic homeostasis at multiple regulatory levels [42]. Complementing these preclinical findings, a clinical study evaluating *S. cumini* seed powder supplementation in patients with poorly controlled type 2 diabetes mellitus demonstrated significant improvements in glycemic parameters over 90 days. Fasting plasma glucose decreased by 9%, 18%, and 30% at 30, 60, and 90 days, respectively, while postprandial glucose declined by 8%, 15%, and 22%. HbA1c levels were significantly reduced from 8.99 ± 1.39% to 8.31 ± 1.40% ($P < 0.05$), whereas no significant improvement was observed in the control group [43]. Together, these experimental and clinical data reinforce the capacity of *S. cumini* phytochemicals to modulate glucose metabolism, insulin sensitivity, oxidative stress, and inflammatory pathways, supporting their relevance within a multi-target framework for diabetes management. Future research should involve in vitro validation of compound-target interactions using relevant cell models, such as placental trophoblasts or insulin-responsive cell lines. Furthermore, in vivo studies in PGD animal models are necessary to evaluate the physiological effects, safety profile, and dosage optimization of *S. cumini* extract or its isolated constituents. Studies should also explore the influence on fetal outcomes, given the maternal-fetal interface is a key concern in PGD.

4. Conclusion

This integrative investigation combining phytochemical profiling, network pharmacology, and molecular docking provides a systems-level understanding of the antidiabetic potential of *S. cumini* bark in the context of pre-gestational diabetes (PGD). The dual-platform metabolomic analysis (GC-MS and LCHRMS) confirmed the presence of chemically diverse bioactive constituents, including flavonoids, fatty acids, and phytosterols, which are widely recognized for their metabolic regulatory properties. Network pharmacology mapping of sixteen selected phytoconstituents against PGD-associated genes revealed central regulatory nodes such as PPAR-γ, glucose transporter (GLUT) proteins, insulin receptor substrates, and pathways involved in insulin signaling and lipid metabolism. These findings reinforce the multifactorial nature of PGD as a network-driven metabolic disorder rather than a single-target condition. Molecular docking analysis further validated the structural plausibility of these interactions, demonstrating strong binding affinities of flavonoids, particularly quercetin, myricetin, and kaempferol, and phytosterols such as ergosta-5,22-dien-3-ol acetate toward key metabolic targets. The convergence of network topology and docking affinity supports a coordinated multi-target mechanism involving modulation of insulin sensitivity, enhancement of glucose uptake, inhibition of carbohydrate-digesting enzymes, and regulation of lipid homeostasis. Such multimodal activity is particularly relevant in PGD, where chronic insulin resistance and dyslipidemia precede pregnancy and contribute to adverse maternal and fetal outcomes. While experimental validation in pregnancy-specific models remains necessary, this study establishes a mechanistic foundation for the therapeutic exploration of *S. cumini* bark. By integrating systems pharmacology with structural interaction analysis, the present work advances beyond reductionist paradigms and highlights *S. cumini* as a promising source of complementary, multi-pathway modulators for managing the complex metabolic dysregulation characteristic of pre-gestational diabetes.

5. Declarations

5.1. Author Contributions

Conceptualization, P.S., A.S., and T.N.S.; methodology, P.S., A.S., and T.N.S.; validation A.S., T.N.S., and H.S.; investigation, P.S. and A.S.; writing—original draft preparation, P.S., A.S., H.S., and T.N.S.; writing—review and editing, P.S. and A.S.; supervision, A.S., H.S., and T.N.S. All authors have read and agreed to the published version of the manuscript.

5.2. Data Availability Statement

The data presented in this study are available in the article.

5.3. Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

5.4. Acknowledgments

The authors would like to thank the Ministry of Health of the Republic of Indonesia and Poltekkes Kemenkes Aceh for supporting this research.

5.5. Institutional Review Board Statement

Not applicable.

5.6. Informed Consent Statement

Not applicable.

5.7. Declaration of Competing Interest

The authors declare that there are no conflicts of interest concerning the publication of this manuscript. Furthermore, all ethical considerations, including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancies have been completely observed by the authors.

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