**RESEARCH ARTICLE**

# Prediction of the Mechanism of *Nephrolepis cordifolia* (L) C. Presl against Disorders of Increased Blood Sugar and Lipid Levels using the Network Pharmacology Approach

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**ABSTRACT**
Elevated blood sugar and lipid levels are a growing global health concern and N. Cordelia presents potential therapeutic benefits. Therefore, this study aimed to identify active compounds and mechanisms in N. cordifolia using a network pharmacology method. Active compounds were screened for target proteins associated with elevated blood sugar and lipids through PPI networks, enrichment analysis, docking, and MM/GB (PB) SA. The results showed 6 compounds from N. cordifolia, and 24 proteins were obtained using Cluster One analysis at the PPI network stage. An important mechanism, such as the PPAR signaling pathway was identified through enrichment. The proteins in this mechanism were FABP, PPARα, and PPARλ, obtained by docking and MMGB (PB) A. The key compounds were 9-Oxo-10 (E) and 12 (E)-octadecadienoic acid, suggesting the potential of N. cordifolia to overcome increased blood sugar and lipids.
**Keywords:** *N. cordifolia*; Network Pharmacology; Blood sugar; Lipid.
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## INTRODUCTION

Elevated blood sugar and lipid levels are commonly associated, especially in conditions such as metabolic syndrome, type 2 diabetes, and lipid disorders[1]. In people with high blood lipid levels, including high triglycerides or low density lipoprotein (LDL) cholesterol, insulin resistance often develops, impacting blood sugar regulation. This phenomenon is prevalent in cases of dyslipidemia, a condition signified by an imbalance in blood lipid levels[2]. Particularly, high triglyceride levels can promote inflammation which disrupts blood sugar control by impairing pancreatic cells' ability to produce insulin[3]. Fatty acid-binding proteins (FABPs) are essential for binding and transporting fatty acids. Disruption in this process lead to fat accumulation within cells, especially in the liver, contributing to insulin resistance and elevated blood sugar levels[4]. Furthermore, lipoproteins such as LDL and very low density lipoprotein (VLDL) reduce the effectiveness of insulin receptors on surface of cells when present in high concentration, thereby raising blood sugar levels[5]. In this context, a plant with promising potential to address blood sugar issues associated with blood lipid imbalances is *Nephrolepis cordifolia*. Research on *N. cordifolia* removes free radicals with an efficiency of 67.02% at a concentration of 30 μg/ml[6]. It also reduces inflammation with an efficiency of 82.66% at a concentration of 500 μg/ml. By increasing the excretion of Cl-, K+, and Na+, the rhizome extract of the plant show diuretic ability[7]. Based on observation, *N. cordifolia* has antibacterial activity against *S. pneumoniae* and *V. parahaemolyticus* and has overcome liver inflammation as well as reduce the occurrence of necrosis[8]. The Banjar tribe in Kalimantan traditionally uses *N. cordifolia* for managing diabetes, as a diuretic, contraceptive, and for treating liver disorders. Studies on species in the Nephrolepis genus, such as *N. exaltata*, have shown that nanosilica inhalation lowers blood sugar levels[9]. Additionally, an ethanol extract from the leaves of *N. undulata*, administered at 800 mg/kg body weight, has been found to reduce blood sugar levels elevated by alloxan, lower cholesterol and LDL triglycerides, and increase high-density lipoprotein (HDL) levels[10]. Further study on *N. undulata* ethanol extract has showed its ability to reduce blood glucose levels induced by streptozotocin (STZ) while enhancing antioxidant activity, seen through decreased malondialdehyde (MDA) levels and increased superoxide dismutase (SOD) and catalase

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activity[11]g. After treatment with CTZ, the ethyl acetate fraction of *N. undulata* had more ameliorative ability than the methanol extract and n-hexane fraction[12]. Therefore, this study aimed to identify the mechanism and active compounds of *N. cordifolia* that have the potential to overcome disorders of increased blood sugar and lipids.

## MATERIAL AND METHODS

*Materials*

This study used 62 compounds derived from *N. cordifolia*[13].

*Tools*

The tools adopted were NCBI (https://pmc.ncbi.nlm.nih.gov/), Genecards (https://www.genecards.org/), and SwissTargetPrediction (http://www.swisstargetprediction.ch/). Similarity ensemble approach (https://sea.bkslab.org/), SwissADME(http://www.swissadme.ch/index.php), Protox 3.0 (https://tox.charite.de/protox3/), ADMETlab 2.0 (https://admetmesh.scbdd.com/), String 12.0 (https://string-db.org/), Venn (https://www.statskingdom.com/venn-

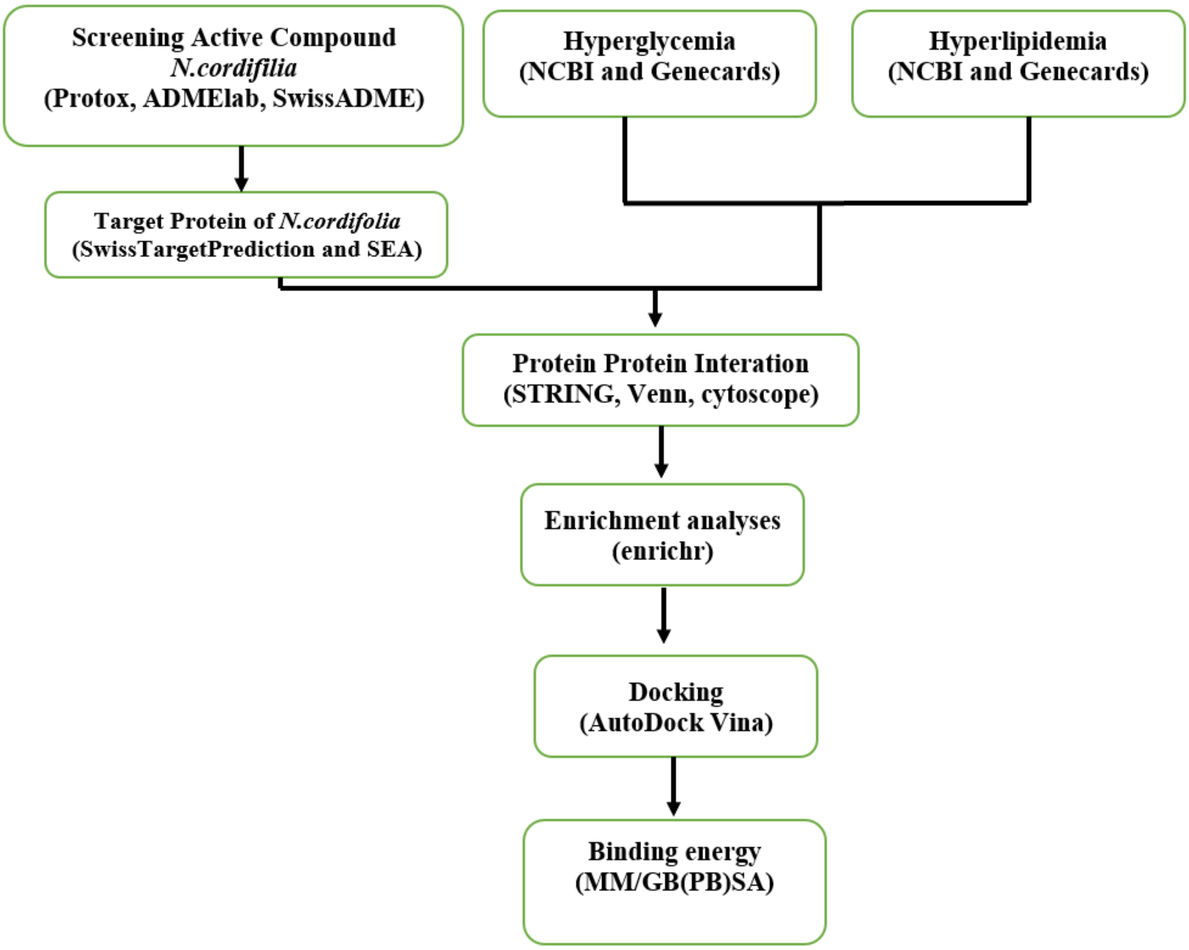


Figure 1: Study scheme

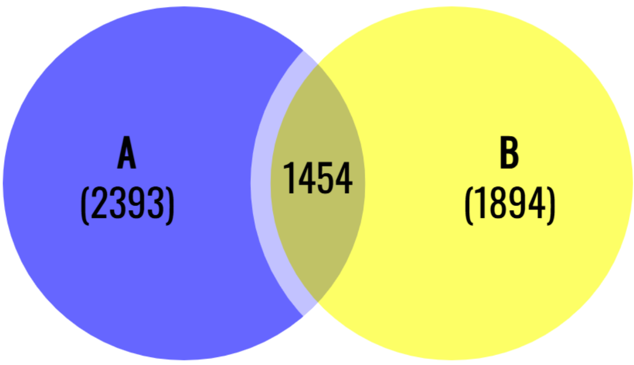


Figure 2: Proteins associated with increasing blood sugar and lipids. * Blue color: proteins associated in increasing blood sugar; and yellow color: proteins involved in increasing blood lipids.

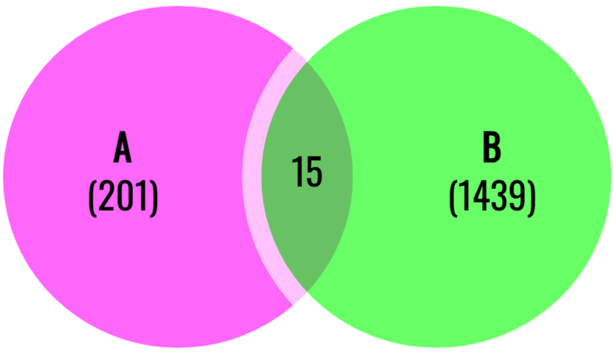


Figure 3: Target proteins of N. cordifolia are associated with increased blood sugar and lipids. *Purple represents the target proteins of N. cordifolia, while green denotes proteins associated with increased blood sugar and lipids.

Table 1: Physicochemical properties of 6 compounds related to increased lipid and blood sugar levels

| Comp. No. | Compound Name | Class | LD50 (mg/kg) | HIA | Biovaibility | mr | H aceptor | H donor | TPSA 140Å) | M LogP |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Glycylglutamic acid | 6 | 6838 | 0.084 | 0.022 | 204.18 | 6 | 4 | 129.72 | -1.53 |
| 2 | α-Aminoadipic acid | 6 | 6830 | 0.09 | 0.002 | 161.16 | 5 | 3 | 100.62 | -2.8 |
| 3 | N-acetyl-L-2-aminoadipic acid | 5 | 5000 | 0.6 | 0.206 | 203.19 | 5 | 3 | 103.7 | -0.4 |
| 4 | 9-Oxo-10(E),12(E)-octadecadienoic acid | 5 | 3200 | 0.014 | 0.092 | 294.43 | 3 | 1 | 54.37 | 3.5 |
| 5 | navenone A | 4 | 830 | 0.045 | 0.008 | 225.29 | 2 | 0 | 29.96 | 2.12 |
| 6 | 6-Quinolinecarboxylic acid | 5 | 3720 | 0.011 | 0.024 | 173.17 | 3 | 1 | 50.19 | 1.34 |

Table 2: Shows the docking results using AutoDock Vina

| Comp. No. | FABP | | PPARα | | PPARλ | |
|---|---|---|---|---|---|---|
| | Docking score (kcal/mol) | Dissoc. Constant (pM) | Docking score (kcal/mol) | Dissoc. Constant (pM) | Docking score (kcal/mol) | Dissoc. Constant (pM) |
| 1 | -5.709 | 65350288 | -5.903 | 47102464 | -5.594 | 79349400 |
| 2 | -4.969 | 227863472 | -5.448 | 101522672 | -4.863 | 272504544 |
| 3 | -6.147 | 31202490 | -5.995 | 40328004 | -5.542 | 86628368 |
| 4 | -6.676 | 31202490 | -6.516 | 16738197 | -6.283 | 24802756 |
| 5 | -3.214 | 4406631936 | -7.004 | 7345137.5 | -6.821 | 10020138 |
| 6 | -6.755 | 11181996 | -6.926 | 8378662.5 | -6.167 | 30166788 |

Table 3: Presents the binding energy calculation using the MM/GB(PB)SA FABP method.

| Compound Number | Van der Waals | Electrostatic | Polar Solvation | Non-Polar Solvation | Gas | Binding Energy (kcal/mol) |
|---|---|---|---|---|---|---|
| 1 | -26.8443 | -8.8552 | 12.107 | -4.01176 | -35.6996 | -27.6044 |
| 2 | -21.5812 | -1.9191 | 6.4179 | -3.43829 | -23.5003 | -20.5207 |
| 3 | -26.5894 | -4.9792 | 9.6136 | -4.24898 | -31.5687 | -26.2041 |
| 4 | -33.9325 | -7.2461 | 9.4752 | -6.63302 | -41.1787 | -38.3365 |
| 5 | -4.1733 | -2.3503 | 6.7939 | -5.6487 | -6.5236 | -5.3784 |
| 6 | -21.4006 | -1.6798 | 4.6895 | -3.31254 | -23.0803 | -21.7033 |

Table 4: Presents the calculation of binding energy using the MM/GB(PB)SA PPARα method.

| Compound No. | Van der Waals | Electrostatic | Polar Solvation | Non-Polar Solvation | Gas | Binding Energy (kcal/mol) |
|---|---|---|---|---|---|---|
| 1 | -27.3201 | -6.0287 | 11.3775 | -4.21447 | -33.3488 | -26.1858 |
| 2 | -20.7066 | -12.2359 | 15.4115 | -3.63965 | -32.9426 | -21.1707 |
| 3 | -29.4807 | -5.4925 | 10.0745 | -4.3689 | -34.9732 | -29.2676 |
| 4 | -45.0403 | -1.8848 | 5.5988 | -6.37072 | -46.9252 | -47.6971 |
| 5 | -31.1455 | -2.2428 | 6.3609 | -5.67147 | -33.3884 | -32.699 |
| 6 | -23.2118 | -1.139 | 4.7422 | -3.36718 | -24.3509 | -22.9759 |

diagram-maker.html), Enrichr (https://maayanlab.cloud/Enrichr/), Kegg pathway (https://www.kegg.jp/), Cytoscape v3.9.1, Marvin Bean, Autodock4, Discovery Studio, and Gromac 2021 were also utilized.

*Method*

*Compound screening*

Protox was used to detect the toxicity of compounds with a minimum class limit of 5 and a dose of 2000 mg/kg Bw. Subsequently, ADMETlab was adopted to screen for bioavailability above 30% and ease of absorption in the gut, while SwissADME was used to evaluate the compounds for oral drug similarity[14].

*Target proteins from N. cordifolia*

The screening of target proteins that can be influenced by compounds from *N. cordifolia* was conducted using SwissTargetPrediction, with a minimum probability limit ≥ 3.00, and the Similarity ensemble approach (SEA), with a TC limit ≥ 3.00. Proteins are associated with increasing blood sugar and lipid levels. Proteins associated with

Table 5: Presents the energy calculation using the MM/GB(PB)SA PPARλ method.

| Compound Number | Van der Waals | Electrostatic | Polar Solvation | Non-Polar Solvation | Gas | Binding Energy (kcal/mol) |
|---|---|---|---|---|---|---|
| 1 | -27.9275 | -3.5109 | 9.5982 | -4.24887 | -31.4383 | -26.089 |
| 2 | -22.4106 | -2.837 | 10.5328 | -3.6827 | -25.2476 | -18.3975 |
| 3 | -29.635 | -1.8361 | 7.3044 | -4.59878 | -31.4711 | -28.7655 |
| 4 | -40.3208 | -2.2738 | 7.562 | -7.0365 | -42.5946 | -42.0691 |
| 5 | -32.0847 | 0.2158 | 3.5747 | -5.24647 | -31.8689 | -33.5407 |
| 6 | -20.6513 | 0.1271 | 2.9631 | -3.16685 | -20.5243 | -20.7281 |

Table 6: Lists the residues amino acid associated in the interaction.

| Compound Number | FABP | PPARα | PPARλ |
|---|---|---|---|
| native | ALA75; ARG106; PRO38; ILE104; ALA33; ALA36; VAL25; GLU72; ASP76; CYS117 | SER280; HIS274; LEU321; MET355; CYS278; PHE318; TYR334; VAL324; ALA333; GLU286 | GLY284; CYS285; LEU270; ILE281; ARG288 |
| 1 | TYR128; LYS58; SER53; THR60 | TYR215; ASN220; MET221; SER323; ILE317 | TYR327; LYS367; TYR473; CYS285 |
| 2 | SER55; THR60 | TYR215; SER323; GLU286; ASN222 | SER289; HIS449; GLN286 |
| 3 | ARG126; SER53 | TYR215; SER323; THR283; MET320 | SER289; TYR327; LYS367; GLN286 |
| 4 | ARG126; TYR128; VAL25; ALA33; PRO38; ALA75; MET20; PHE16; TYR19 | ASN220; MET221; THR279; SER280; VAL324; MET320 | LYS367; ALA292; ARG288; ILE326; ILE326; LEU330; HIS323 |
| 5 | THR102; PHE57; VAL23; VAL25; ALA33; ALA75; MET20; PHE16; TYR19; ALA36; PRO38 | ASN222; SER323; THR279; VAL324; MET320; LEU321; ILE317; MET355 | HIS449; CYS285; ARG288; ALA292; ILE326 |
| 6 | PRO38; PHE16 ; MET20; ALA75; ALA33; ASP76 | TYR215; SER323; VAL324; MET320 | ARG288; ILE326; LEU330; ALA292; ILE326 |

increased blood glucose and lipid levels were identified by searching for the keywords "hyperglycemia" and "hyperlipidemia" on NCBI and Genecards.

*The N. cordifolia protein network influences the elevation of blood sugar and lipid levels.*

A Venn diagram was used to connect proteins from *N. cordifolia* and those increasing blood sugar and lipids using a Venn diagram, thereby obtaining an intersection. The results were then analyzed using the STRING database to create a protein-protein interaction (PPI network), with the organism specification being homosapiens. The interaction was visualized through a cytoscope to obtain the core of the proteins which were analyzed using the Cytocluster_ClusterOne mode in cytoscape[15]. Furthermore, the proteins used were included in the first group, with the lowest P value. The next analysis comprised dividing the Degree Centrality (DC) into 3 categories, namely 2-9, 10-14, and 15-222, as well as Closeness Centrality (CC) and radiality.

*Sieving*

Proteins related to *N. cordifolia* and increased lipid and blood sugar levels were further analyzed to identify related biological processes, molecular functions, cellular components, and signaling pathways. This analysis utilized the Enrichr and KEGG PATHWAY databases[16] with a P value of ≤0.01.

*Docking and analysis of MM/GB(PB)SA*

In this study, docking was conducted using the AutoDock Vina method[17]. Proteins engaged in the process were downloaded from the RCSB database, namely 2nnq, 6I96, and 2prg for FABP, PPARα, and PPARλ, respectively. FABP redocking began by removing the $SO_4$ water molecule. The docking coordinates were X: 3.64, Y: 8.51, and Z: 17.21, with BMS-309403 as the native ligand. PPARα was redocked by removing water molecules, as well as chains B and C. The docking coordinates were X: -33.21, Y: 27.59, and Z: 7.84. while the native ligand used was pemafibrate. PPARλ was redocked using chain A only with rosiglitazone as the native ligand and coordinates of X: 46.18, Y: -44.86, and Z: 16.96. The docking process yields a score in units of kcal/mol and a Dissoc. Constant in pM. It was important to acknowledge that a smaller docking score corresponded to a lower Dissoc. Constant. The MM/GB(PB)SA surface area method was adopted to calculate the binding energy of the selected protein-ligand complex in addition to the docking score. This method, which calculates the Van der Walls, electrostatic, polar-nonpolar, and gas solubility values was adapted from gromacs. Furthermore, it was among the most reliable

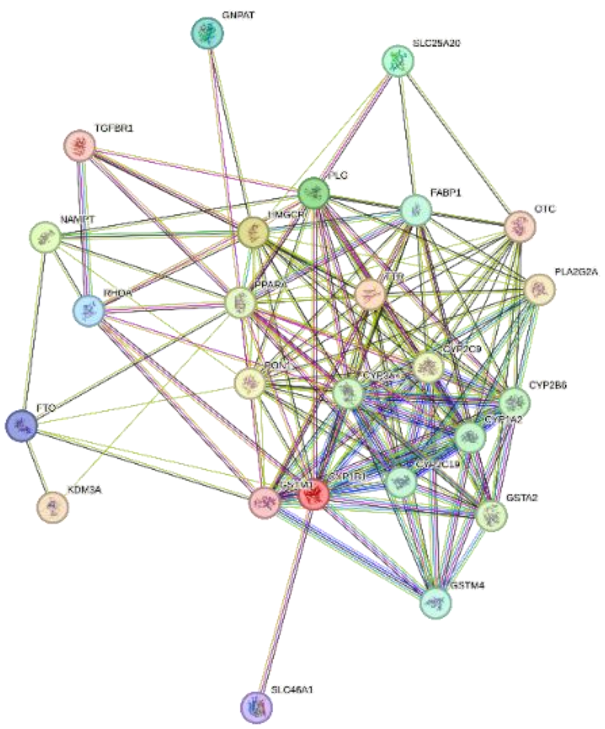


Figure 4: PPI network of String

endpoint methods for calculating the free energy of protein-ligand interaction binding[18].

*Data analysis*

The docking results were analyzed using docking scores and Gibbs energy, then continued with binding energy MM/GB(PB)SA from gromacs by calculating polar, and non-polar solvents, gases, and charges.

## RESULTS

*Compound Screening*

Research on *Nephrolepis cordifolia* identified 62 compounds, which underwent an initial screening using Protox to exclude those with toxic potential, yielding 39 compounds deemed non-toxic. Subsequent analysis in ADMETlab evaluated these compounds for intestinal absorption and bioavailability, refining the selection to 11 promising candidates. In a final step, SwissADME was employed to compare the physical and chemical properties of these 11 compounds with those of existing oral drugs, confirming their similarity and potential suitability for further study.

*Target proteins from N. cordifolia*

Proteins were screened for potential interactions with the 11 compounds identified. Using SwissTargetPrediction, 1 protein was obtained, while SEA produced 216 target proteins. Duplicates were removed to finalize the list of 216 unique targets.

*Proteins are involved in increasing blood sugar and lipid levels.*

The NCBI identified 854 proteins associated with increased blood sugar, while genecards showed 3730. After processing to prevent data duplication, 3847 proteins were obtained. For those affecting elevated blood lipid levels, Genecards identified 3263, and NCBI reported 356, leading to 3348 proteins after duplicate removal. Subsequently, screening was conducted using a Venn diagram to identify proteins that affected increased blood sugar and lipids. The process led to 1454 proteins associated with the 2 factors, as shown in Figure 2.

*The N. cordifolia protein network influences elevated blood sugar and lipid levels.*

*N. cordifolia* compounds interacted with 216 target proteins, of which 15 were associated with increased blood sugar and lipids, as shown in Figure 3. Among the 11 compounds from the plant, only 6 showed significant effects across the proteins obtained. The physicochemical properties of the 6 compounds are shown in Table 1, while the string's PPI network, comprising 25 nodes and 149 edges is presented in Figure 4. Data were analyzed using the Cytocluster_ClusterOne method obtained from the cystoscope, as shown in Figure 5, and the protein derived was SLC46A1. This analysis produced the smallest P value compared to other clusters, with 24 nodes, a density of 0.5362, and an internal weight of 148. Degree Centrality (DC) was categorized into DC 2–9 (GSTM4, RHOA, FTO, NAMPT, TGFBR1, SLC25A20, KDM3A, and GNPAT), DC 10–14 (OTC, GSTA2, and PLA2G2A), and DC 15–22 (PPAR, HMGCR, CYP1B1, PON1, TTR, CYP3A4, CYP2C9, CYP1A2, PLG, CYP2B6, FABP1, GSTM1, and CYP2C19). The correlation between DC 2-9 and CC was 0.5111 - 0.5609, while the radius was 0.9565-0.9644. The correlation between DC 10-14 and CC was 0.6571 - 0.741935484 and was associated with Radiality: 0.9762 - 0.9841. Finally, the correlation between DC15-22 and CC 0.7419 - 0.9583 was associated with Radiality: 0.9841 - 0.9980.

*Sieving*

Based on the sieving analysis using enrichr, various data were produced, as shown in Figure 7. The biological process analysis identified 76 data with a P value of less than 0.01. Analysis of cellular components produced 9 data points, while molecular function produced 15. The Kegg pathway analysis yielded 23 distinct pathways, where *N. cordifolia* reduces blood sugar and lipid levels through the PPAR signaling pathway shown in Figure 6 with the code map03320. The targeted proteins were FABP, PPARα, and PPARλ, as presented in Figure 8.

*Docking and MM/GB(PB)SA*

Screening results show that *N. cordifolia* influences blood sugar and lipid levels by activating the PPAR signaling pathway. The primary proteins affected include the upstream FABP and the downstream PPARα and PPARλ. Compounds from *N. cordifolia* target these proteins through docking interactions. The RMSD values for the native ligands bound to FABP, PPARα, and PPARλ are 0.8291 Å, 1.9847 Å, and 1.5099 Å, respectively, all meeting docking validation criteria with values below 2. Table 2 presents docking scores against FABP, with values ranging from -6.775 kcal/mol to -3.214 kcal/mol, while the native ligand's redocking score is -7.473 kcal/mol, indicating a stronger binding than the plant's ligands. For PPARα, the docking score of the compound is -3.097 kcal/mol, smaller than the native ligand's score. The docking score against PPARλ is lower than that of the native ligand at -5.529 kcal/mol, except for α-Aminoadipic acid. Further analysis using MM/GB(PB)SA, which factors in charge, solubility, and gas interactions, yields diverse binding energies, as shown in Table 3.

The binding energy for FABP native ligand is -33.8509 kcal/mol, while the binding energies of the ligands from *N. cordifolia* are generally higher, except for ligand no. 4, which is -38.3365 kcal/mol. For PPARα, the native ligand binding energy is -4.59579 kcal/mol. Meanwhile, for PPARλ, the binding energies for ligands no. 4 and no. 5 are -42.0691 kcal/mol and -33.5407 kcal/mol, respectively, compared to the native ligand's energy of -31.3917 kcal/mol. Table 6 details the residues engaged in these interactions, providing further insight into the binding

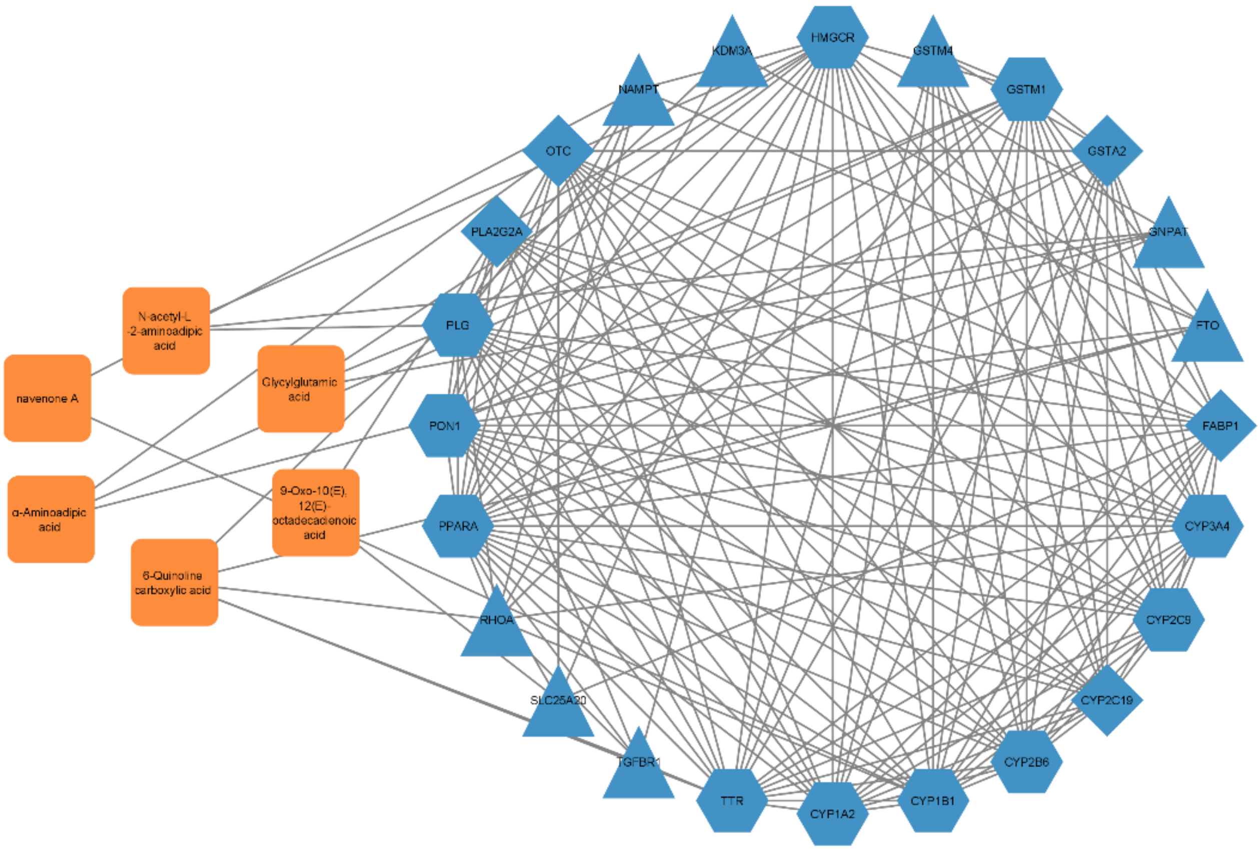


Figure 5. ClusterONE analysis

*Orange Round Rectangle: Compound N. Cordifolia; Blue: proteins affected by N. cordifolia in overcoming increased blood sugar and lipids; observation based on Degree_Centrality. DC2-9: triangle; DC10-14: diamond; DC15-22: hexagon.

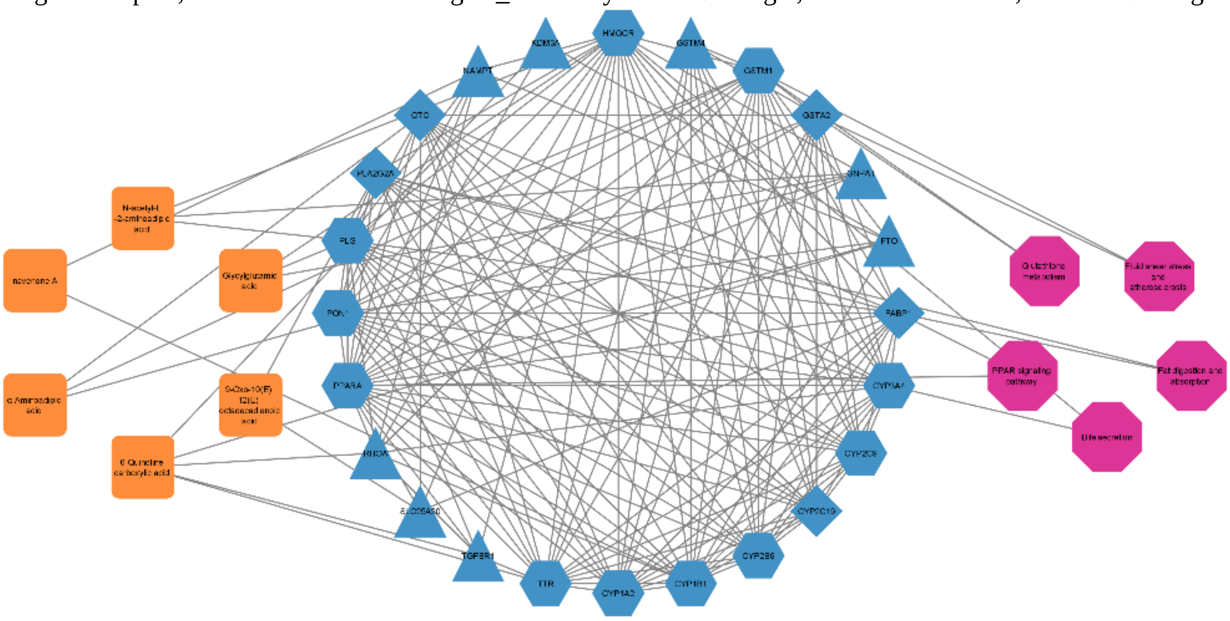

Figure 6. Screening of the N. Cordifolia Mechanism

*Orange: compound N. cordifolia; blue: proteins; purple: mechanism.

dynamics across the proteins. Figure 9 presents ligands with potential protein interactions.

Compared to the native ligand, the *N. cordifolia* ligand that binds FABP shows specific residue interactions in ligand no. 4 with VAL25, ALA33, PRO38, and ALA75, and in ligand no. 5 with VAL25, ALA75, ALA36, and PRO38. Ligands no. 1, 2, and 3, as well as ligands no. 6, feature different residues upon binding to FABP. For PPARα, *N. cordifolia* ligands interact through various residues, namely GLU286 in ligand no. 2, SER280 in ligand no. 4, VAL324 in ligand no. 5, and both MET355 and VAL324 in ligand no. 6, with no shared residues in ligands 1 and 3. The ligands also show 6 distinct interactions with PPARλ. Ligand no. 1 shares the CYS285 residue with the native ligand, while ligand no. 4 corresponds at ARG288, and ligand no. 5 again at CYS285. Ligand no. 6 also shares residues with the native ligand. Based on MM/GB(PB)SA docking analysis, 9-Oxo-10(E),12(E)-octadecadienoic acid was the most favorable ligand for FABP, PPARα, and PPARλ, given its lowest binding energy, which enables strong interaction with the target proteins. As presented in Figure 9, this ligand forms a hydrogen bond with FABP, acting as a hydrogen donor to TRY128:OH and a hydrogen acceptor from ARG126:HH21. It also establishes

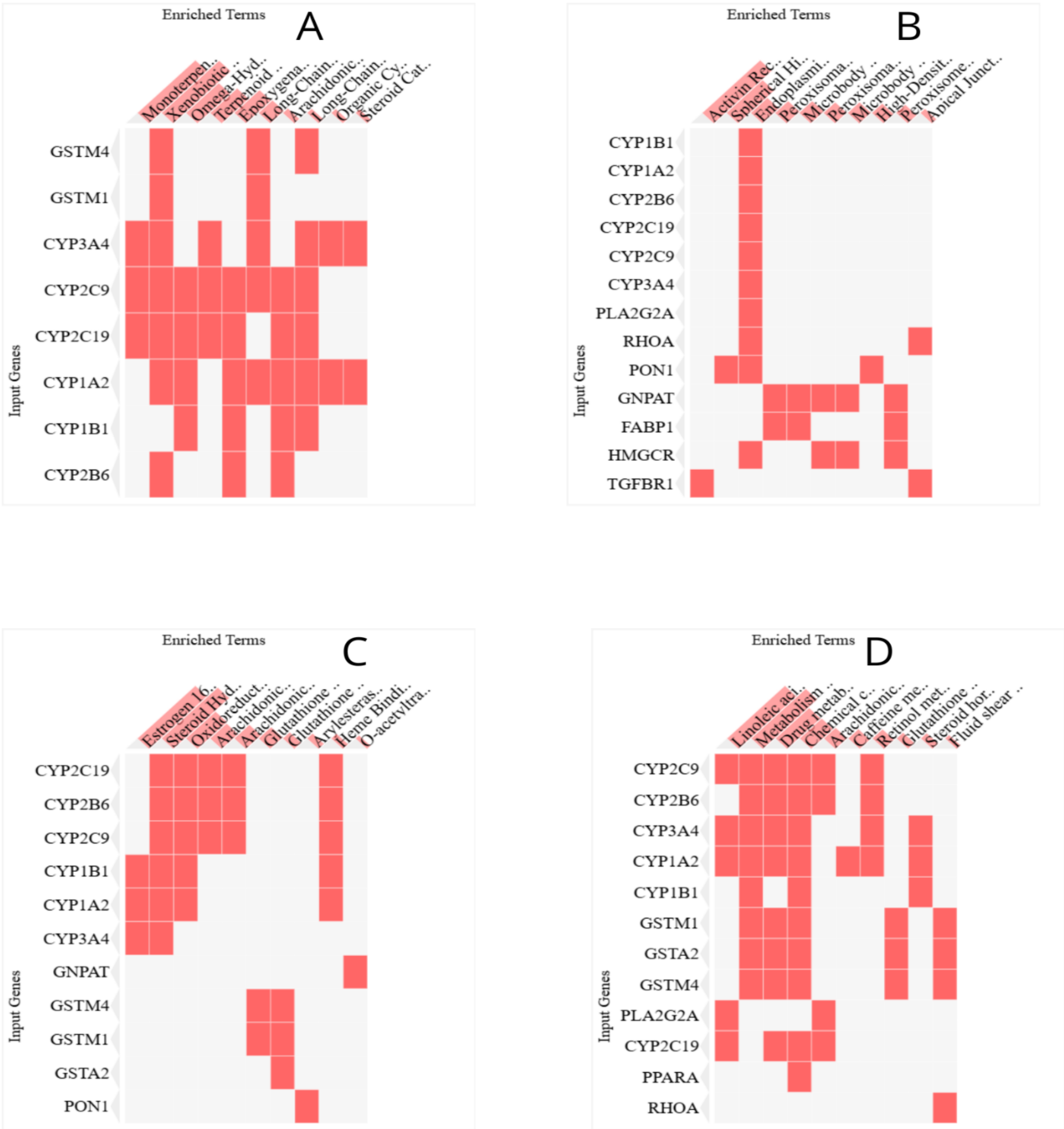


Figure 7. Clustergram Screening.
*A: Biological process; B: Cellular component; C: Molecular function; D: Kegg Pathway

hydrophobic interactions with VAL25, ALA33, PRO38, ALA75, MET20, PHE16, and TYR19. In binding to PPARα, the ligand forms hydrogen bonds, donating to THR279:OG1 and SER280:OG, while accepting from ASN220:H, MET221:H, and SER280:HA. Additionally, it forms hydrophobic bonds with VAL324 and MET320. For PPARλ, the ligand acts as a hydrogen acceptor to LYS367:HZ1 and creates hydrophobic bonds with ALA292, ARG288, ILE326, LEU330, and HIS323.

## DISCUSSION

Based on the network pharmacology analysis and screening that has been conducted, the predicted mechanism of *N. cordifolia* was obtained. The plant was predicted to lower blood glucose and lipids through the PPAR signaling pathway, identified by the code map03320. The targeted proteins were FABP, PPARα, and PPARλ comprised in the DC15-22 group.

Fatty acid-binding protein (FABP) plays a role in regulating lipid and glucose metabolism in the body. It helps transport fatty acids in cells and influences the use of lipids in the body as an energy source. Glucose metabolism is impacted by disruption in lipid metabolism and influenced blood sugar levels. Numerous studies have shown that high FABP levels may be associated with insulin resistance and impaired glucose metabolism[19].

Cellular signals that change the expression of genes associated with energy metabolism is controlled by FABP. As a result, the balance between the use of glucose and lipids as fuel for the body is altered[20]. The metabolism of lipid, carbohydrate, and protein is regulated by PPARs which when activated by ligands, bind to the RXR (retinoid X receptor) receptor, forming a complex that regulates target gene expression. This pathway is essential in various biological processes, including regulation of fat levels, control of blood sugar levels, and inflammation[21]. Among the examples of PPARs, PPARα facilitates fatty acid oxidation in the liver and muscles, regulates lipid metabolism, and controls cholesterol levels. Agonists such as fibrates typically trigger PPAR activation to reduce blood triglyceride levels[21]. It is important to acknowledge that PPARλ is related to glucose metabolism and fat storage. In the treatment of type 2 diabetes, PPAR-agonists such as thiazolidinediones can enhance insulin sensitivity[22]. Fenofibrate is a drug that acts on the PPARα pathway. It functions by activating the PPARα receptor, which speeds up lipolysis, stimulates lipoprotein lipase, and lowers apoprotein C-III[23]. PPARα, a nuclear receptor, plays a key

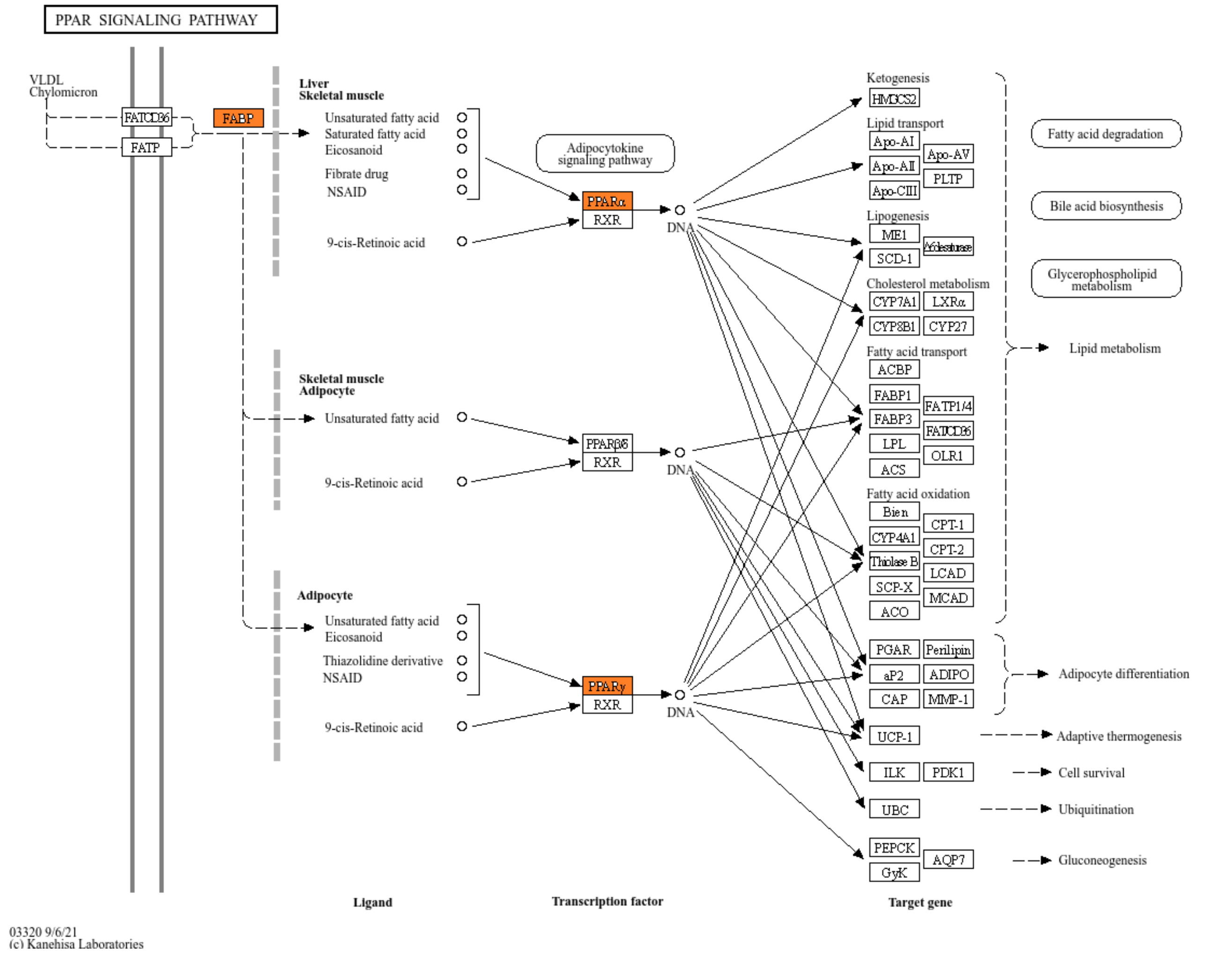


Figure 8. Shows the potential mechanisms of N. cordifolia in lowering blood sugar and lipids through PPAR signalling pathways.* Orange color: N. cordifolia target proteins.

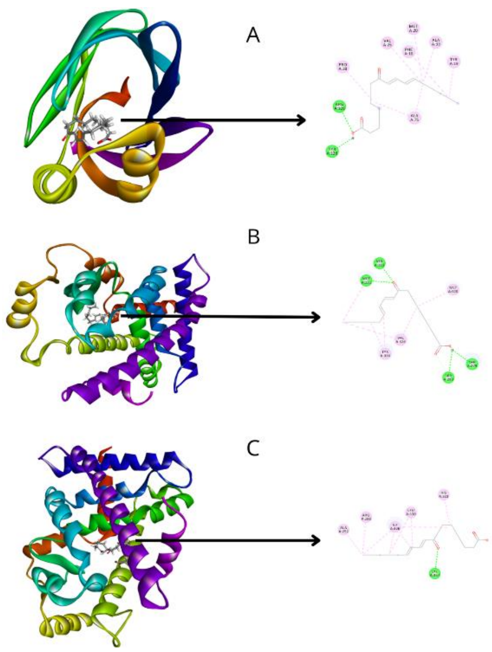

Figure 9. Shows the 3- and 2-dimensional visualisation of 9-Oxo-10(E), 12(E)-octadecadienoic acid interactions with target proteins.
* A: FABP; B: PPARα; C: PPARλ

role in regulating lipid, glucose, and amino acid homeostasis[24].

Drugs that act on PPARλ are lobeglitazone, rosiglitazone, and thiazolidinedione[25]. They enhance sensitivity to insulin by activating the PPARγ receptor, which promotes glucose utilization in skeletal muscle and fat cells, increasing free fatty acid absorption. Concurrently, fat breakdown in adipose tissue is reduced, and hepatic glucose production decreases[26]. Pioglitazone, an agonist for both PPARα and PPARγ, further exemplifies dual pathway activation[27]. Additionally, phenylperiacid binds to FABP, potentially triggering downstream pathway activation[28]. Another research oleic acid also binds to FABP and contributes to cell proliferation[29]. The chemical 9-Oxo-10 (E), 12 (E)-octadecadienoic acid from *N. cordifolia* is very similar to oleic acid based on the structural pattern.

**CONCLUSION**

In conclusion, during the screening process, 6 compounds were obtained from *N. cordifolia*, associated with high blood sugar and lipid levels. Additionally, 15 proteins were discovered, and at the PPI network stage with ClusterOne analysis, 24 were identified. At the enrichment stage, the PPAR signaling pathway was a key mechanism, with proteins such as FABP, PPARα, and PPARλ. Through docking and analysis using MM / GB (PB) SA method, 9-Oxo-10 (E), 12 (E) -octadecadienoic acid was identified as a promising active compound from *N. cordifolia* within this pathway. Since this study was limited to a model, further validation was needed using in vitro and in vivo methods.

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