

Prediction of *Nephrolepis cordifolia* (L.) K. Presl Mechanism as Hyperlipidemia Using Network Pharmacology, Docking and DFT Method

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ABSTRACT

As the prevalence of hyperlipidemia, a major risk factor for cardiovascular disease, continues to rise, there is a pressing need for safer and more effective alternative treatments. The molecular mechanism by which *Nephrolepis cordifolia* (L.) K. Presl exerts its antihyperlipidemic action is unknown, however reports of this activity have been made. Using a mix of network pharmacology, molecular docking, and density functional theory (DFT) analysis, this study sought to explain how active chemicals in *N. cordifolia* against hyperlipidemia work. Various methods were employed, such as pharmacophore- and Lipinski-based active compound selection, disease prediction using bioinformatics databases, protein-protein interaction (PPI) analysis, Enrichr signaling pathway screening, and docking and density-functional theory (DFT) against the primary target proteins. Seven compounds out of sixty-two made it through the selection process, according to the results. Additionally, ellagic acid, gallic acid, and 6-methyl-2-pyridinemethanol were the three primary chemicals that had the most promise for interacting with hyperlipidemia target proteins, including EGFR, AKT1, and IGF1R. Based on DFT studies, ellagic acid exhibited the lowest HOMO-LUMO energy and docking score of any of these molecules, suggesting the strongest affinity and most stable contact. According to the signal pathway analysis, the compound's mode of action was largely influenced by the following pathways: endocrine resistance, PI3K-Akt, and MAPK signaling, all of which are involved in regulating lipid metabolism. Through the appropriate multi-target molecular processes, this work demonstrates that *N. cordifolia* may be a natural source of therapy for hyperlipidemia

Keywords: Hiperlipidemia, *Nephrolepis cordifolia*, network pharmacology, molecular docking, DFT

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INTRODUCTION

Elevated blood lipid levels, or hyperlipidemia, are a risk factor for a number of cardiovascular illnesses, including atherosclerosis, coronary heart disease, and stroke ¹. Hyperlipidemia is on the rise around the world as a result of people leading sedentary lives and eating a lot of saturated fat. An alarming number of people have excessive total cholesterol levels, according to epidemiological statistics from a variety of countries ². There is a significant death rate from cardiovascular disease, and more than 39% of individuals have raised cholesterol levels, according to a research by the World Health Organization (WHO). Myopathy and reduced liver function are common side effects of using synthetic medicines like statins as main therapy ³. Because of this, there is a pressing need for safer and more effective natural-based treatments for decreasing blood cholesterol levels.

This past decade has seen a meteoric rise in the amount of research into alternative medicine and natural cures. *Nephrolepis cordifolia* (L.) K. Presl is a medicinal herb with antihyperlipidemic effects. There has been some evidence that ethanol extract of *N. undulata* leaves, namely at doses of 200, 400, and 800 mg/kg BW, may lower total, low-density lipoprotein, and cholesterol levels while increasing HDL, according to previous research on the genus *Nephrolepis* ⁴. The high flavonoid content of *N. exaltata* leaves was accompanied by an anti-lipid peroxidation ability of 0.04 µg/ml ⁵. Research from different species suggests that some flavonoids, such as naringenin and apigenin-7-O-neohesperidoside from *A. Iva* (L.) and luteolin from *T. kirilowii*, can reduce cholesterol levels ⁶. Hence, a network pharmacology approach is required to determine the hyperlipidemia-reducing mechanism and signaling pathway of *N. cordifolia* active chemicals. Docking and density functional theory (DFT) further

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enhance the approach by analyzing the binding energies of chemicals to target proteins, leading to hyperlipidemia. So, the purpose of this research is to find out how DFT, network pharmacology, and docking work to treat hyperlipidemia.

There is currently a lack of comprehensive knowledge on the molecular mechanisms of the active chemicals found in many herbal plants, despite their examination as potential antihyperlipidemic therapeutic options. Bioinformatics tools like network pharmacology are applicable here ⁷ computational chemistry, and other cutting-edge techniques are being employed more and more to investigate the pharmacological effects of natural substances ⁸. In line with the multifaceted nature of metabolic disorders like hyperlipidemia, network pharmacology permits the discovery of active drugs with several targets and pathways ⁹. When used in conjunction with molecular docking and density-functional theory (DFT), this approach can accurately depict molecule binding ¹⁰ regarding the consistency of ligand-protein complexes ¹¹. Antihyperlipidemic treatment derived from *N. cordifolia* requires a solid scientific basis, and the in silico approach is an essential part of that.

METHODS

You may see the study's flowchart in Figure 1.

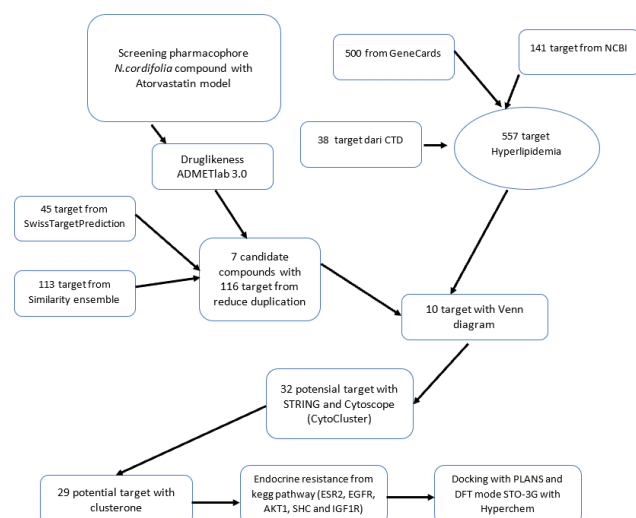


Figure 1. Research flowchart

Screening of active compounds of *N. cordifolia*

Past research has yielded a total of sixty-two chemicals derived from *N. cordifolia* ¹². The evaluation began with pharmacophores, specifically Aromatic (X: 10.1755; Y: -0.0458; Z: 0), Hydrogen donor (X: 10.8565; Y: 2.3649; Z: 0), and Hydrogen acceptor (X: 12.2578; Y: 1.3468; Z: 0), with atorvastatin as a comparison. Then, using Lipinski's Rule principle, the evaluation continued with the similarity of oral drugs (ADMETlab 3.0_ <https://admetlab3.scbdd.com/>).

Target prediction of *N. cordifolia*

The PubChem database was used to obtain the conical smile of each compound that was chosen (<https://pubchem.ncbi.nlm.nih.gov/>), produced by analyzing the molecular formula of the substance. We used Swiss Targets Prediction to determine which chemical targets each of these compounds occupied (<http://www.swisstargetprediction.ch/>) which is more likely than 2 ¹³ on top of the Similarity Ensemble Method (SEA; <https://sea.bkslab.org/>) having a Tanimoto score greater than 0.25 ¹⁴. Chemical structural similarity was also a major factor in this database's target prediction technique.

Target prediction of hyperlipidemia disease

To NCBI, the term "hyperlipidemia" was input (<https://ncbi.nlm.nih.gov/>), Medical IDs (<https://www.genecards.org/>), CTD, as well as (<https://ctdbase.org/>) in order to identify disease targets. Only "Homo sapiens" were the intended subjects of the research. A closer proximity to the disease was associated with a higher predicted target relevance score in GeneCards. Scores above the median were experimentally assessed as possible targets where there were many indicated. The 500 most relevant ratings were utilized in this study ¹⁵, and CTD's Inference Score was over 50 ¹⁶.

Protein-Protein Interaction

The links between targets and biological processes were investigated through protein-protein interaction (PPI) analysis. The data gathered from the Venn diagram between hyperlipidemia and possible targets of *N. cordifolia* were used to generate this interaction. Using String, we examined gene connections (<http://string-db.org/>, version 11.0). With a confidence score of 0.4, a stringency FDR value of 50%, and an organism restriction to "Homo sapiens," the database used text mining and integrated trials to predict and extract PPIs. Hidden isolated nodes represent proteins that do not interact with one another. Cytoscape was used to display the molecular component network and any interactions in order to generate the PPI network. The results were exported as "TSV" format ¹⁷. Nevertheless, PPI network interpretation was seen as challenging owing to its complexity, highlighting the necessity for supplementary suitable analytical techniques. CytoCluster classifies network nodes into clusters according to shared attributes or patterns of interaction, then uses those clusters to find related sub-networks or modules. To forecast the network's principal targets and biological processes, the study is coupled with Gene Ontology (GO) enrichment analysis. Because of this, understanding the PPI network is made easier and more accurate ¹⁸, given that degree, eccentricity, closeness, centrality (CC), and radiality are the basis of target grouping.

GO and KEGG pathway analysis

One popular approach to discovering genes' shared roles using biological ontologies is KEGG. Both KEGG and GO use directed acyclic graph structures to annotate genes for pathways and biological processes and molecular functions and cellular components, respectively. Both the GO and KEGG enrichment were evaluated using a stringent criterion of a P value <0.05 <https://maayanlab.cloud/Enrichr/>.

Docking and DFT

Docking

The PLANTS Computational program was used for all molecular docking¹⁹. Proteins were thought of as stiff molecules and ligands as flexible ones in the rigid docking method. Protein binding pockets were examined using the Biovia Discovery Studio application. A crystal structure with the following coordinates: X: 28.0319, Y: 5.22134, Z: 10.8912, and a radius of 12.518 Å was subsequently retrieved from the Protein Data Bank (AKT1, 4ekl). The X, Y, and Z coordinates of EGFR (5ug8) are -13.7156, 15.3976, and -26.7021, with a radius of 11.7701 Å. IGF1R (5u8q) and SHC (1n3h) both have coordinates of X:22.3885; Y:8.1497; Z:113.678, with a radius of 11.31 Å. ESR2 (1qkm) has coordinates of X:22.3885; Y:3.8699; Z:3.36999. A redocking of the natural ligand onto proteins was done to validate the molecular docking approach. The RMSD value of the native ligand with the redocking result being less than 2.0 Å was used to determine the validity of this approach. At the same time, BIOVIA Discovery Studio was used to conduct the 2D and 3D protein-ligand interactions.

DFT

The first step was to use HyperChem's editor to construct the molecular structure, checking that its geometry was in accordance with the target chemical structure. Afterwards, the molecular mechanics method (MM+) was used to optimize the initial geometry, which was then saved as a starting point for density-functional theory (DFT) analysis²⁰. After configuring the computation settings, the DFT method was chosen with the STO-3G basis set. We also optimized the geometry using DFT and double-checked our results to make sure we were utilizing the least amount of energy possible. In addition, molecular parameters such as total energy, electron density distribution visualization, and HOMO and LUMO orbital energies were analyzed²¹

RESULTS AND DISCUSSIONS

Screening of active compounds of *N. cordifolia* (Active compounds from *N. cordifolia*)

Seven active compounds were isolated from *N. cordifolia* according to Lipinski's Rule and pharmacophore selection (Aromatic Coordinate, Hydrogen donor, and Hydrogen acceptor of atorvastatin molecule; see Table 1). The following criteria were used for this selection: MW ≤ 500, H acceptor ≤ 10, H donor ≤ 5, and M log value < 4.5, with a maximum of two infractions allowed.

Table 1. Physicochemical properties of 7 compounds screened from *N. cordifolia*

Name	MW	H acceptor	H donor	TPSA	MLog P
5-Hydroxymethyl-2-furaldehyde	126.0316	2	1	33.12	0.212

6-Methyl-2-pyridinemethanol	123.0685	2	1	33.12	0.447
Deferiprone	139.0627	3	1	42.23	-0.514
SCHEMBL2 2498716	237.0634	6	3	95.86	-0.014
Gallic acid	170.0216	5	4	97.99	0.692
Ellagic acid	302.0059	8	4	141.34	0.951
Desethylatrazine	187.0632	5	3	76.72	1.421

Target prediction of *N. cordifolia* (Target of compound)

Swiss Target Prediction was used to identify seven compounds with a probability larger than 0.2, and 45 targets were obtained from this process. We were able to extract 113 targets from SEA that had a Tc value greater than 0.25. The final result after merging and eliminating duplicates was 116 targets.

Prediction of hyperlipidemia disease (target of disease)

We used the GeneCards, NCBI, and CTD databases to find hyperlipidemia targets. We obtained 500 with the greatest relevance score based on GeneCards. We got 38 data points from CTD and 141 from NCBI. There were 557 hyperlipidemia targets found in this study's integration of the three disease databases.

Protein-protein interaction

Ten shared targets were identified by combining the targets of *N. cordifolia* (116 genes) with hyperlipidemia (557 genes) in a Venn diagram (Figure 2.A). The last step was to analyze the three *N. cordifolia* chemicals and ten genes using a network (Figure 2.B). In order to do PPI analysis, this target was uploaded to STRING (Figure 3.A). Cytoscape analysis yielded data from 32 nodes with 233 edges (Figure 3.B). According to Figure 2.A, 29 target compounds were obtained from the PPI module analysis using CytoCluster, with the exception of AKR1B1. Figure 3B shows that four nodes, representing EGFR, AKT1, KDR, and IGF1R, were part of the target grouping based on the Degree value > 21, eleven nodes were part of the 16–20 grouping, and fifteen nodes were part of the 11–15 grouping. With a value of 2, two groups were obtained based on Eccentricity. The CC values ranged from 0.5714 to 0.9333, while the radiality values were 0.9711 to 0.9972, corresponding to 17 targets. With CC values between 0.5185 and 0.5384 and Radiality values between 0.9642 and 0.9670, Value 3 has three targets: SELL, SORT1, and TTR.

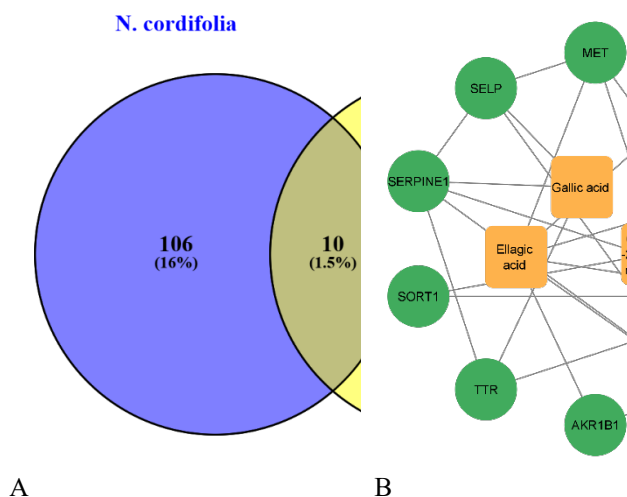


Figure 2: A. Venn diagram between targets of *N. cordifolia* and hyperlipidemia. B. Target interactions between *N. Cardifolia* and hyperlipidemia.

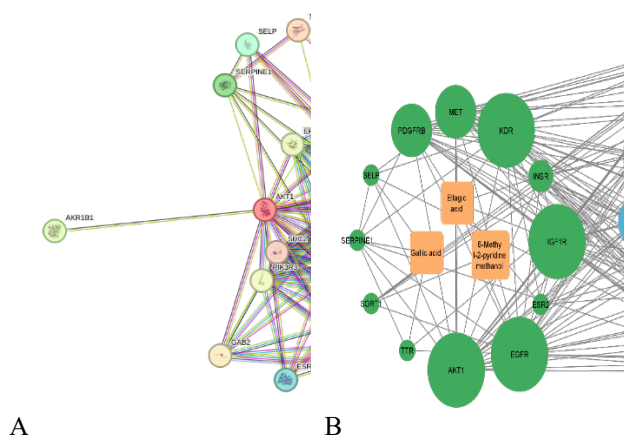


Figure 3: A. Target interaction of hyperlipidemia from string-db.org. B. Interaction between *N. Cardifolia* target and hyperlipidemia using Cytoscape. The larger the diameter of the target, the more important the target is.

GO and KEGG pathway analysis

GO

The 29 targets were analyzed using Enrichr with a P-value less than 0.05 for Biological Process (BP), Cellular Component (CC), and Molecular Function (MF) ²². The most important factor in controlling metabolic activities, blood pressure (BP) revealed a peak value of 425. Goto:0007169 was the first grouping; it dealt with membrane tyrosine kinase receptor signals. Second place went to MF with a score of 71; this factor was associated with molecular binding and the functioning of several enzymes and receptors (GO: 0004714). A variety of vesicles, lumens, and membranes were included in CC with the lowest value of 46, indicating membrane tyrosine kinase activity. In terms of protein kinase complexes, the highest CC value was GO: 1902911.

KEGG

As demonstrated in Figure 4, Cytoscape was used to visualize the intricate interactions among the active components of *N. cordifolia*, targets, and pathways. Ellagic acid was the primary compound estimated to have a significant impact on hyperlipidemia treatment; its Degree, CC, Radiality, and Eccentricity values were 8, 0.5441, and 0.9746, correspondingly. The next substance was gallic acid, which has the following properties: degree = 3, CC = 0.3775, radiality = 0.9500, eccentricity = 4, and degree = 1 with CC = 0.3490, radiality = 0.9434, and eccentricity = 4. The primary docking targets were the top three nodes in the network based on degree. Some of them included EGFR (Degree=33; CC=0.9024; Radiality=0.9935; Eccentricity=2), AKT1 (Degree=30; CC=0.9024; Radiality=0.9934; Eccentricity=3), and IGF1R (Degree=3; CC=0.7708; Radiality=0.99909; Eccentricity= 3). The involvement of signaling pathways in systems pharmacology was also critical, since they connected receptor-ligand interactions to pharmacodynamic results. Six of the 136 pathways found throughout the investigation were associated with hyperlipidemia. In terms of degree, the primary pathways were as follows: hsa04014 (Ras signaling pathway), hsa04151 (PI3K-Akt signaling pathway), hsa04010 (MAPK signaling pathway), hsa04015 (Rap1 signaling pathway), hsa01522 (endocrine resistance), and hsa04066 (HIF-1 signaling pathway). Because it is the primary kegg pathway leading to dyslipidemia, this study zeroed attention on the endocrine resistance pathway as it relates to docking and DFT ²³, with hyperlipidemia as its direct cause ²⁴, as illustrated in Figure 5.

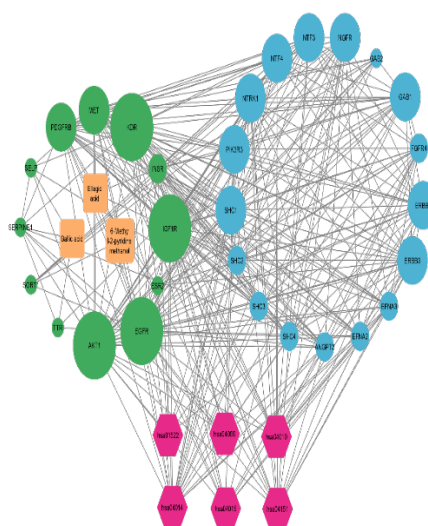


Figure 4: Interaction between *N. Cardifolia* targets and hyperlipidemia using Cytoscape which has been through pathway screening using <https://maayanlab.cloud/Enrichr/>.

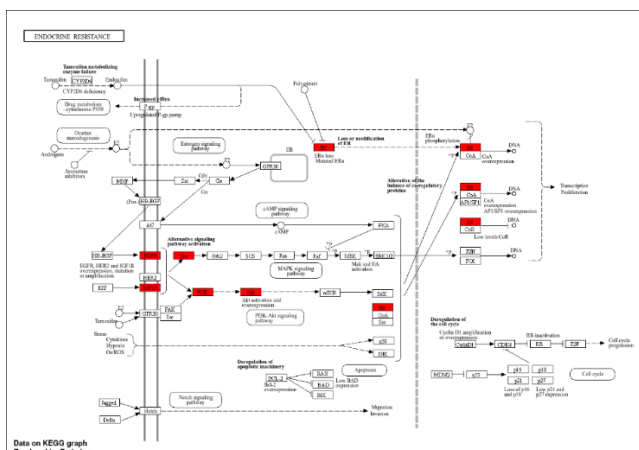


Figure 5. Endocrine resistance pathway

“The red color is the target affected by *N. cordifolia*.”

Docking and DFT

Docking

The active chemicals found in *N. cordifolia* that were expected to impact hyperlipidemia were gallic acid, ellagic acid, and 6-Methyl-2-pyridinemethanol. In order to dock with ER (ESR2), EGFR, AKT1, SHC, and IGF1R, these chemicals were utilized. Water molecules and other ligands that would not be used in the docking process were eliminated beforehand. A stiff protein occupied by an active ligand conformer was one of the docking modes tested in this study. Validation was conducted using native ligand redocking, with the test ligand's coordinates derived from those of the native ligand. The natural ligand's validation results against ESR2, EGFR, and AKT1 were 1.831 Å, 1.724 Å, and 1.132 Å, correspondingly. Because this value was less than 2 Å, it satisfied the validation value, and the test ligand was able to utilize the native ligand's coordinates. Due to the lack of a native ligand for SHC and IGF1R, the docking locations used in this investigation were predicted using <https://open.playmolecule.org/>. As the docking score decreases, the conformation becomes more stable and the response probability increases. Table 2 shows the docking results, and figure 6 shows that ellagic acid had the lowest score. According to the results, the target protein was most strongly anticipated to react with ellagic acid, gallic acid, and 6-Methyl-2-pyridinemethanol in that order. The high degree of homology between the bound residues of ellagic acid and the native ligand supported its poor docking score. The same residues—HIS475, LEU298, LEU476, ALA302, and MET336—are bound by ellagic acid in ESR2. Met793, ALA743, LEU844, VAL726, and LEU718 are among its EGFR interactions. Residues ALA230, VAL164, MET281, ALA177, MET227, and LYS179 are frequent AKT1 interactors.

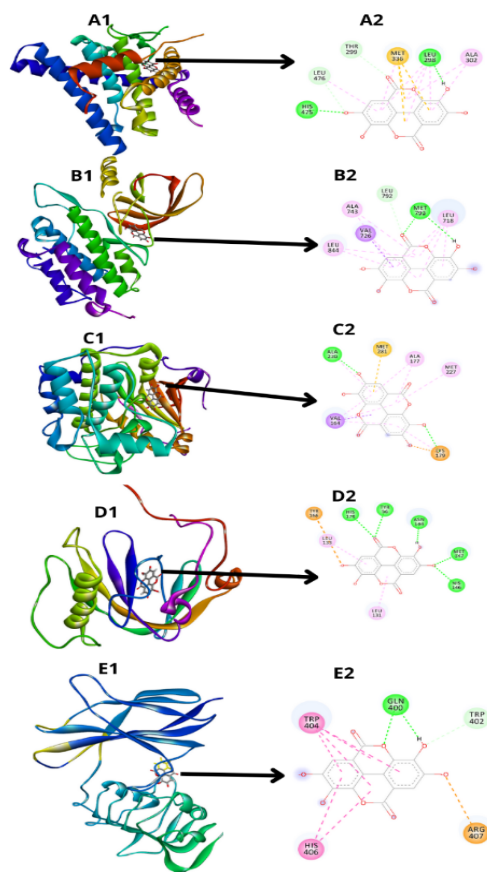


Figure 6. Interaction between ellagic acid and target protein

*1 is a three-dimensional interaction; 2 is a two-dimensional interaction; A: interaction between ellagic acid and ESR2; B: interaction between ellagic acid and EGF; C: interaction between ellagic acid and AKT1; D: interaction between ellagic acid and SHC; E: interaction between ellagic acid and IGF1R

Table 2. Docking scores and residues involved in docking of targets in endocrine ristance.

Protein	Compound	docking score	Residu asam amino
ER (ESR2)	native	- 94.5 275	ARG346; HIS475; LEU339; LEU476; LEU298; PHE356; ALA302; LEU343; MET336
	6-Methyl-2-pyridinem ethanol	- 59.7 026	ARG346; LEU339; GLU305; PHE356; ALA302; MET336; LEU343 MET340:SD
	Gallic acid	- 63.9 36	ARG346; GLU305; LEU339; PHE356; LEU298; ALA302

	Ellagic acid	-74.8099	HIS475; LEU298; THR299; LEU476; ALA302; MET336
EGFR	native	-108.239	MET793; CYS797; GLY796; LEU718; GLN791; PRO794; MET790; LEU844; VAL726; ALA743
	6-Methyl-2-pyridinem ethanol	-63.687	THR854; ASP855; THR854; CYS775; MET790; VAL726; ALA743; LYS745; CYS775
	Gallic acid	-65.8228	MET793; GLN791
	Ellagic acid	-70.7135	MET793; LEU792; ALA743; LEU844; VAL726; LEU718
AKT1	native	-116.327	ALA230; GLU228; GLY157; TYR229; GLU234; GLU278; LYS158; GLY159; MET281; VAL164; MET227; LYS179; LEU156; ALA177
	6-Methyl-2-pyridinem ethanol	-56.8175	ASP439; LEU156; ASP439; PHE236; GLU234 (elektrostatik)
	Gallic acid	-62.062	GLU234; GLU278; ASN279; LYS179
	Ellagic acid	-70.3072	ALA230; VAL164; MET281; ALA177; MET227; LYS179(salt bridge)
SHC	native	0	0
	6-Methyl-2-pyridinem ethanol	-67.1233	SER154; SER151; TYR166; LY155; TRP38
	Gallic acid	-60.7962	SER154; ALA165; SER151; TYR166; GLY155; ILE150; ALA153
	Ellagic acid	-68.5045	TYR56; HIS146; MET147; HIS178; ASN144; LEU131; LEU133; TYR166 (elektrostatik)
IGF1R	native	0	0
	6-Methyl-2-pyridinem ethanol	-59.6146	GLN400; TRP404; TYR508

	Gallic acid	-65.3752	GLN400; LEU401; TYR508; TRP402; ARG407 (salt bridge)
	Ellagic acid	-73.7882	GLN400; TRP402; ARG407 (elektrostatik)

DFT

Molecular structure optimization was performed on all three compounds in the DFT investigation using HyperChem in conjunction with the STO-3G database. With an electronic energy of -953016.3105 kcal/mol, a hydration energy of -29.67 kcal/mol, and a difference between the HOMO and LUMO energies of 0.29129 eV, ellagic acid had the lowest energy of -556449.0000 kcal/mol according to these studies. Table 3 shows the whole data from the DFT analysis, which proves that ellagic acid combines with the target protein more easily than other chemicals.

Table 3. DFT analysis of three active compounds of *N. cordifolia*

Name	Total energy (kcal/mol)	Electronic energy (kcal/mol)	nuclear energy (kcal/mol)	hydration Energy (kcal/mol)	LUMO eV	HOMO eV
6-Methyl-2-pyridine methanol	-202654.1544	-408572.0485	205917.8941	-4.88	-23.1228	-21.9513
Gallic acid	-348161.0605	-747704.3452	399543.2847	-24.24	-14.7636	-13.754
Ellagic acid	-556449.0000	-953016.3105	396567.6471	-29.67	-15.2988	-15.0075

Ellagic, gallic, and oleanolic acids are among the bioactive components found in *N. cordifolia*. This agrees with earlier research that found fern to be an abundant source of phenolics, flavonoids, and triterpenoids including oleanolic acid and β -sitosterol, which have multiple medicinal uses, such as hepatoprotective and antioxidant effects²⁵. The synergistic action of these chemicals lends credence to the idea that they regulate lipid metabolism and act as antioxidants, hence preventing hyperlipidemia. In vitro evidence of the antioxidant and anti-inflammatory properties of *N. cordifolia*²⁶, additionally bolster the potential for a shielding impact against dyslipidemia. The in silico results corroborate the published phytochemical evidence and pharmacological activity, providing a scientific basis. In doing so, it demonstrates the connection

between the computational approach and preexisting experimental data from the lab.

Through network pharmacology, it was demonstrated that the active molecule of *N. cordifolia* operates through the PI3K-Akt, AMPK, and SIRT1 pathways. It is evident that the chemicals work together in a synergistic fashion. Consistent with previous findings, an extract mixture of *A. membranaceus*, *H. rhamnoides*, and *T. mongolicum* reduced the pAKT/AKT and pPI3K/PI3K ratios in HepG2 cells while increasing the pAMPK/AMPK and SIRT1 ratios²⁷. The results show that one of the most important goals of hyperlipidemia treatments based on plants is to control signaling pathways. Conditions involving dyslipidemia are associated with changes in these pathways' regulation of energy metabolism, lipid oxidation, and cellular stress responses. Molecular effects that have a beneficial effect on metabolism in animal models are comparable to the successful docking of ellagic acid to targets like AKT1, EGFR, and IGF1R²⁸. Computational modeling thus yields molecular mechanisms that are consistent with the biological outcomes of previous investigations.

Consistent with earlier findings, this work identifies ellagic acid as the principal molecule exhibiting antioxidant and metabolic activity, as well as the ability to control lipid profiles in metabolic syndrome animal models. It has been demonstrated in non-alcoholic liver illnesses that ellagic acid's microbiotic metabolites, urolithins, help reduce inflammation and oxidative stress^{29,30,31,32}. The pharmacokinetic profile (restricted absorption rate and plasma half-life <1 hour after oral treatment) and low bioavailability ($9.7 \pm 3.2 \mu\text{g ml}^{-1}$ in water) are the reasons behind this. In order to improve the efficacy in clinical settings, more sophisticated formulation approaches should be considered. These findings open up new possibilities for the research and production of medicinal nanoparticles or standardized extracts derived from ellagic acid in *N. cordifolia*.

CONCLUSION

By utilizing network pharmacology, molecular docking, and DFT approaches, this study concludes that *N. cordifolia* possesses the potential to be an antihyperlipidemic drug. Ellagic acid, gallic acid, and 6-methyl-2-pyridinemethanol are the three primary active chemicals, and they interact strongly with key target proteins like EGFR, AKT1, and IGF1R. According on docking scores and DFT characteristics, ellagic acid demonstrates the most significant activity among these molecules. A number of caveats should be noted, the most notable of which is the lack of experimental validation in vitro or in vivo for the in silico method used in this study. Computer models and prediction databases, such docking and density-functional theory (DFT), have their limits when it comes to depicting actual biological situations. These findings can pave the way for future biochemical and pharmacological experiments that prove *N. cordifolia*'s efficacy and safety as a natural antihyperlipidemic drug.

Author contributions

S.H. is responsible for conceptualization and original draft writing. D.S.: conceptualization. N.K.: writing and editing. A.R.: writing and editing. K.N.: analyzes data and reviews. The authors have read and agreed to the published version of the manuscript.

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Declarations

The authors declare there is no conflict of interest in this study.

Consent for authors publication not displayed

Ethical approval Not implemented in this study.

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