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Network Pharmacology and Molecular Docking Based Prediction of Mechanism of Pharmacological Attributes of Glutinol

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Abstract: Glutinol, a triterpenoid compound, has no documented systematic investigation into its mechanism. Hence, we used network pharmacology to investigate glutinol's mechanism. The chemical formula of glutinol was searched in the PubChem database for our investigation. The BindingDB Database was utilized to discover probable glutinol target genes after ADMET analysis with the pkCSM software. DAVID tools were also used to perform Gene Ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of target genes. We also uploaded the targets to the STRING database to obtain the protein interaction network at the same time. Then, we performed some molecular docking using glutinol and targets. Finally, we used Cytoscape to visualize and evaluate a protein–protein interaction network and a drug-target-pathway network. Glutinol has good biological activity and drug utilization, according to our findings. A total of 32 target genes were discovered. Bioinformatics and network analysis were used, allowing the discovery that these target genes are linked to carcinogenesis, diabetes, inflammatory response, and other biological processes. These findings showed that glutinol can operate on a wide range of proteins and pathways to establish a pharmacological network that can be useful in drug development and use.

Keywords: *Acacia nilotica*; asthma; network pharmacology; molecular docking

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1. Introduction

Plants are important natural resources for both traditional and modern therapeutic systems all throughout the world. Plants and plant derivatives have been used for medicinal purposes for thousands of years [1]. The existence of a large group of active components in medicinal plants, such as alkaloids, triterpenoids, essential oils, and phenolic compounds, contributes to their curative qualities. Plants are utilized as phytomedicine to treat a variety of ailments due to the presence of bioactive constituents [2].

Triterpenoids are one of the most important classes of phytochemicals, with more than 20,000 members identified and recognized thus far [3]. Numerous triterpenoids have been demonstrated to be helpful in experimental tests in recent years and are thought to contribute to the health-promoting qualities of food plants such as fruits, vegetables, and

spices [4]. Despite the fact that triterpenoids were originally thought to be biologically inactive, new information on their various types of pharmacological and biological activities, as well as their low toxicity profiles, has reignited interest in human health and disease [5]. Triterpenoids are used for antipyretic, analgesic, hepatoprotective, anti-inflammatory, sedative, tonic, and cardio tonic properties in a variety of Asian countries [6].

Glutinol, a triterpenoid compound, first isolated from the leaves of Scoparia dulcis, possesses pharmacological attributes including anti-diabetic [7], anti-inflammatory [8] and anti-cancer [9] properties. To evaluate the anti-diabetic potential of glutinol, insulin secretory activity on isolated mice islets and MIN-6 pancreatic β-cell line was assessed. Glutinol displayed a moderate insulin secretagogue attribute with percentage inhibition of 137.25 ± 7.63% compared to insulin secretion by glucose of 100 ± 8.33% [10]. Anti-inflammatory potential of glutinol was assessed via its inhibitory potential against cyclooxygenase and nitric oxide. Glutinol displayed significant anti-inflammatory potential with an IC_{50} value of 1.22 µg/mL. Glutinol displayed significant anti-cancer effect against human ovarian cancer cells by altering the P13AKT signaling pathway. The IC_{50} value against human OVACAR3 cells was found to be 6 µM. These diverse pharmacological attributes of glutinol make it a valuable and interesting compound. However, the molecular mechanism responsible for its biological potentials has not been systematically evaluated. Therefore, in the current research, an attempt was made to explore the molecular mechanism of action of glutinol by using a network pharmacology approach. This strategy not only accelerates drug discovery but also saves time, energy, and above all, money. The procedure for glutinol's gene prediction and analysis is shown in Figure 1.

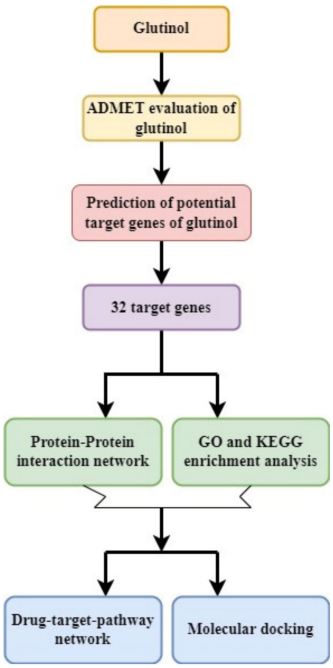


Figure 1. The overall work flow of bioinformatics analysis of glutinol.

2. Methodology

2.1. PubChem Database-Based Screening of Chemical Structure and ADMET Analysis

The PubChem database is a free and open database that houses essential information about drug development and chemical biology research [11]. The chemical formula, SMILES and CAS number of glutinol were found using the term "glutinol" in the search box. Then, using the online application pkCSM, ADMET analysis was performed for glutinol.

2.2. Target Gene Screening by Using Binding DB Database

Binding DB (https://www.bindingdb.org/bind/index.jsp, accessed on 10 April 2022), was used to predict target genes for discovered chemicals using the "homo sapiens" setting and SMILES [12]. The target genes were screened in Binding DB by setting the "minimum needed interaction score" to "high confidence (0.700)" throughout the prediction process.

2.3. Protein–Protein Interaction Network Construction and Analysis

STRING 11.0 is an online database that can collect, assess, and integrate information regarding protein–protein interactions from all publicly available sources (https://string-db.org/, accessed on 10 April 2022) [13]. It can enhance existing data on protein–protein interactions with computational predictions. The STRING database now has 32 additional potential glutinol targets. To create a protein interaction network, the species was set to Homo sapiens and the minimum interaction score was set to 0.7. For visual analysis, the findings were loaded into Cytoscape 3.7.2 (https://cytoscape.org, accessed on 10 April 2022).

2.4. Analysis of Gene Function and Pathway Enrichment

The Gene Ontology (GO) function and KEGG pathway enrichment of proteins included in the PPI network were analyzed using the Database for Annotation, Visualization, and Integrated Discovery (https://david.ncifcrf.gov/, accessed on 10 April 2022) v 6.8 to elucidate the role of target proteins that interact with glutinol [14].

2.5. Construction of Glutinol-Target-Pathway Network

We used Cytoscape 3.7.2 to create a visual network to help us better comprehend the complicated relationships between glutinol and its targets and pathways.

2.6. Molecular Docking

Chemical Computing Group Inc.'s MOE-Dock (https://www.chemcomp.com, accessed on 10 April 2022) was used to conduct computational experiments in the current work. Protein Data Bank was used to obtain the crystal structures of CCND, ESR1, CYP19A1, HMGCR, and PTPRC (PDB id 2W96, 1GWQ, 3EQM, 2R4F and 5FMV). The crystal structures were edited with the goal of removing water molecules, followed by the addition of hydrogen atoms to the protein, and then energy minimization was performed to reduce clashes, while for structural optimization, MMFF94x force field was employed [15]. The active site was then identified, and dummy atoms were made from the alpha spheres that resulted. RMSD values of less than 1.3 were clustered together in docked positions. For subsequent investigation, a docked complex with the lowest energy-minimized pose was chosen. Ten distinct conformations were carefully selected. The resulting docked complex model was then utilized to calculate the energy parameters and estimate the docked interactions at the active site using the MMFF94x force field energy computation.

3. Results

3.1. Molecular Formula and ADMET Attributes of Glutinol

The chemical formula of glutinol was retrieved from PubChem database, as shown in Figure 1. The ADMET analysis of glutinol, conducted using the pkCSM online tool, fell in the "Accepted" category. These findings indicate that glutinol possesses all drug likeness properties confirmed through ADMET analysis as shown in Table 1.

3.2. Prediction of Glutinol's Target Genes

Potential genes targeted by glutinol were retrieved from BindingDB database. The results revealed 32 target genes linked to glutinol, as shown in Table 2. These target genes were then utilized for further investigations.

Table 1. ADMET analysis of glutinol.

Molecular Weight	Absorption			Distribution		Metabolism		Excretion		Toxicity			
	WS	IS	SP	BBB	CNSP	CYP3A4 Substrate	CYP2C19 inhibitor	TC	MTD	ORAT	HT	SS	AMES
426.72	−6.49	94.41	−2.816	0.665	−1.905	Yes	No	−0.037	−0.603	2.298	No	No	No

BBBP = blood brain barrier permeability (logBBB), CNSP = CNS permeability (log PS), IS = intestinal solubility (%abs), ORAT = oral rat acute toxicity (LD50), SP = skin permeability (log Kp), TC = total clearance (logml/min/kg), WS = water solubility (logmol/L), MTD (Maximum tolerated dose).

Table 2. Potential genes targeted by glutinol.

S. No.	Gene	UniProt ID	Description
1	DHCR24	Q15392	Delta(24)-sterol reductase
2	HMGCR	P04035	3-hydroxy-3-methylglutaryl-coenzyme reductase
3	ACHE	P22303	Acetylcholinesterase
4	AKR1B10	O60218	Aldo-keto reductase family 1 member B10
5	GAA	P10253	Lysosomal alpha-glucosidase
6	CRYAA	P02489	Alpha-crystallin A chain
7	CRYAB	P02511	Alpha-crystallin B chain
8	PRKAA2	P54646	5′-AMP-activated protein kinase catalytic subunit alpha-2
9	AR	P10275	Androgen receptor
10	ALOX15	P16050	Polyunsaturated fatty acid lipoxygenase ALOX15
11	F3	P13726	Tissue factor
12	F10	P00742	Coagulation factor X
13	CYP17A1	P05093	Steroid 17-alpha-hydroxylase/17,20 lyase
14	CYP19A1	P11511	Aromatase
15	LIG1	P18858	DNA ligase 1
16	CDC25B	P30305	M-phase inducer phosphatase 2
17	ESR2	Q92731	Estrogen receptor beta
18	ESR1	P03372	Estrogen receptor
19	GRIN1	Q05586	Glutamate receptor ionotropic, NMDA 1
20	ITGAV	P06756	Integrin alpha-V
21	PTPRC	P08575	Receptor-type tyrosine-protein phosphatase C
22	ELANE	P08246	Neutrophil elastase
23	RELA	Q04206	Transcription factor p65
24	RORC	P51449	Nuclear receptor ROR-gamma
25	OSBP2	Q969R2	Oxysterol-binding protein 2
26	NR1H3	Q13133	Oxysterols receptor LXR-alpha
27	PTPN1	P18031	Tyrosine-protein phosphatase non-receptor type 1
28	F2	P00734	Prothrombin
39	SREBF2	Q12772	Sterol regulatory element-binding protein 2
30	SHBG	P04278	Sex hormone-binding globulin
31	PTPN2	P17706	Tyrosine-protein phosphatase non-receptor type 2
32	VDR	P11473	Vitamin D3 receptor

3.3. Protein–Protein Interaction Network

Target genes of glutinol were imported into the STRING database with the filter of Homo sapiens as species to achieve a protein interaction network. The results were then imported to Cytoscape for results visualization (Figure 2). Circle size and color were

different according to the degree value. There were 42 nodes and 81 edges in the PPI network. Network Analyzer in Cytoscape reported an average node degree value of 3.85, a betweenness centrality value of 0.05, and a closeness centrality value of 0.33. A total of eight nodes had degree values, betweenness centrality, and closeness centrality that were above the average. These could be the key glutinol targets that contribute to its pharmacological effect. These nodes with their names and details are listed in Table 3.

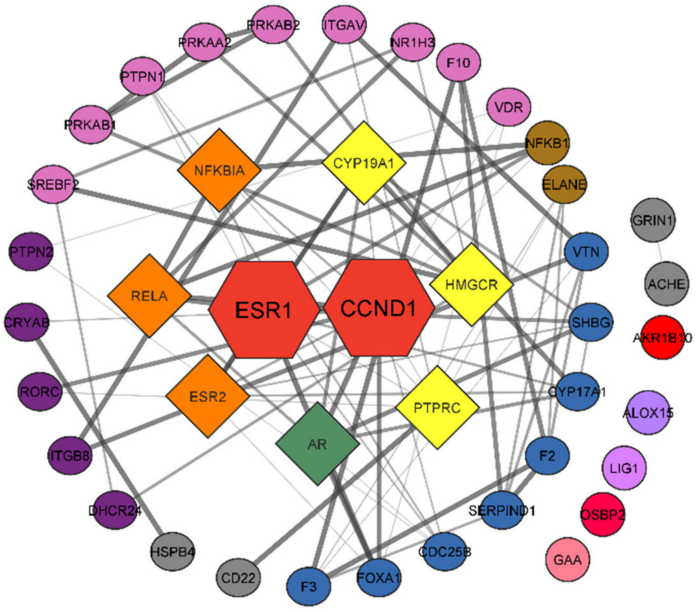


Figure 2. Protein interaction network of glutinol.

Table 3. Major protein interaction network topological parameters.

Name	Degree	Betweenness Centrality	Closeness Centrality
CCND1	13	0.356617	0.507463
ESR1	13	0.243091	0.5
CYP19A1	7	0.253281	0.43038
HMGCR	7	0.242254	0.343434
PTPRC	7	0.420766	0.447368
RELA	6	0.076522	0.404762
ELANE	4	0.192513	0.34
ITGAV	3	0.096702	0.336634

3.4. GO Enrichment Analysis

We used the DAVID tool to perform GO enrichment analysis on the 32 identified genes in order to further investigate them. The Benjamini–Hochberg procedure was used to correct *p*-values, and the top 10 significantly enriched items in the BP, MF, and CC categories were picked based on $P < 0.05$, as shown in Figure 3. BP (42 records), MF (32 records), and CC (15 recordings) accounted for 71.74 percent, 16.67 percent, and 11.59 percent, respectively. Target proteins in the BP category were mostly implicated in steroid metabolic process, intracellular receptor signaling pathway, regulation of inflammatory response, steroid biosynthetic process and organic hydroxyl compound biosynthetic process. The target proteins in the MF category were mostly engaged in steroid binding, nuclear receptor activity ligand activated transcription factor activity, transcription coactivator binding and transcription cofactor binding. The target proteins in the CC category were engaged in

synaptic cleft, external side of plasma membrane, intrinsic component of external side of plasma membrane, cytoplasmic side of membrane and transcription regulator complex.

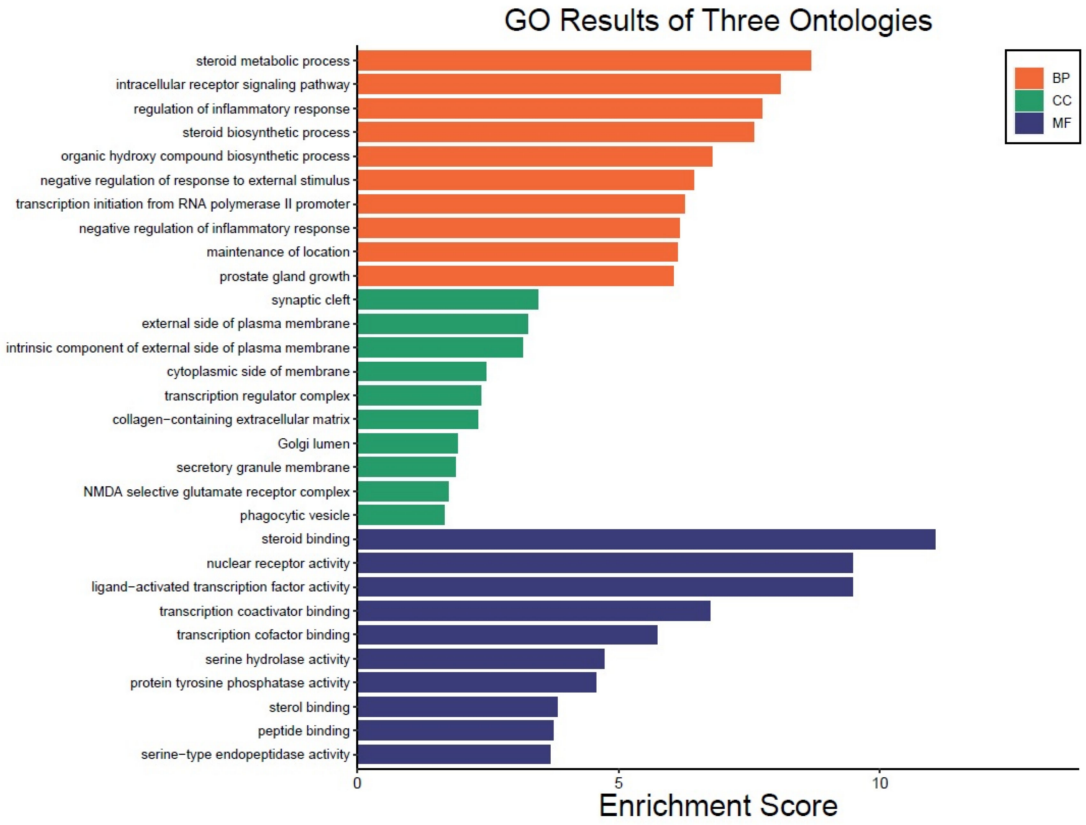


Figure 3. GO enrichment analysis of target genes. Biological Process (BP), Cellular Component (CC), Molecular Function (MF). Height of bar represents number of target genes.

3.5. KEGG Enrichment Analysis

We also ran KEGG enrichment analyses on these candidate genes using the DAVID program. Twenty-nine potential target genes from 32 target genes were found to be enriched in the KEGG pathway enrichment study, and 10 signal pathways were strongly linked to the target genes ($P < 0.05$). The 10 pathways are depicted in Figure 4, along with their enrichment ratios. The pathways that were highly enriched included chemical carcinogenesis-receptor activation (hsa05207), insulin resistance (has04931), prolactin signaling pathway (has04917), and complement and coagulation cascade (hsa04610).

3.6. Network Analysis

We created a drug-target-pathway network diagram using Cytoscape 3.7.2 to highlight the interaction between substance (glutinol), targets, and pathway in greater detail. Figure 5 depicts a network with 40 nodes and 59 edges. The compound was represented by a green circle, targets were represented by red inverted triangles, and pathways by yellow triangles. According to this network, RELA can be considered as the hub gene, as it was enriched in almost all enriched pathways.

3.7. Molecular Docking

It is assumed that ligand–receptor complexes with lower binding energy exhibit strong interactions with receptors. There is currently no universal standard for active molecule target screening. As a starting point for screening, active components with a binding energy of less than −5.0 kJ/mol were chosen. Molecular docking revealed that 5 out of 8 identified target proteins had a glutinol affinity of less than −5.0 kJ/mol. Figure 6 displays the top

five docking outcomes with the lowest binding energy. Table 4 and Figure 6 illustrate the results. Molecular docking results also showed that as compared to other selected genes, CYP19A1 showed significant interaction with glutinol, with a binding energy of −10.1795 kJ/mol. Data about the top ten docked poses of glutinol with selected targets are provided in the supplemental table.

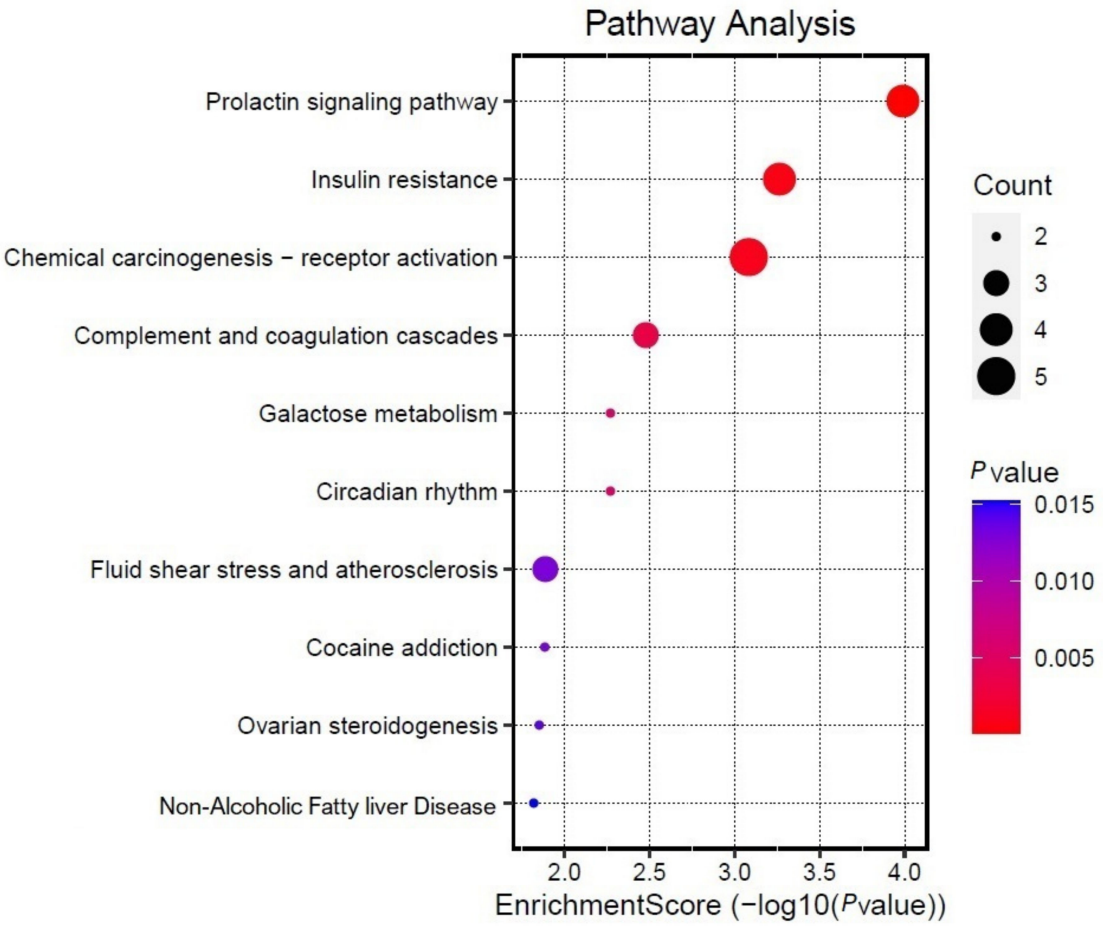


Figure 4. KEGG enrichment analysis of target genes.

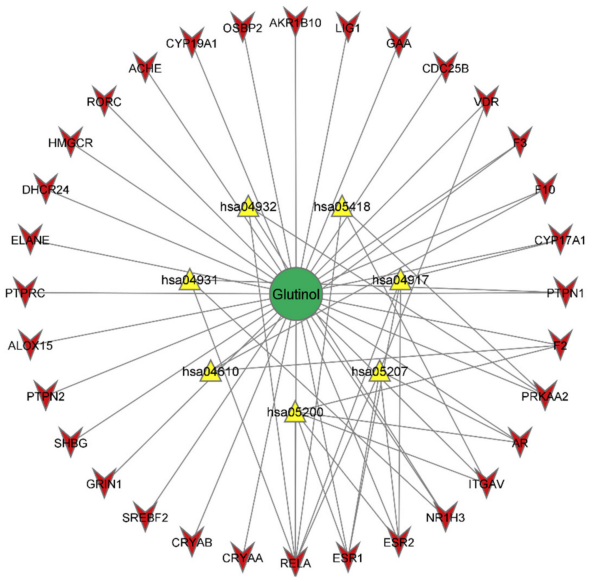
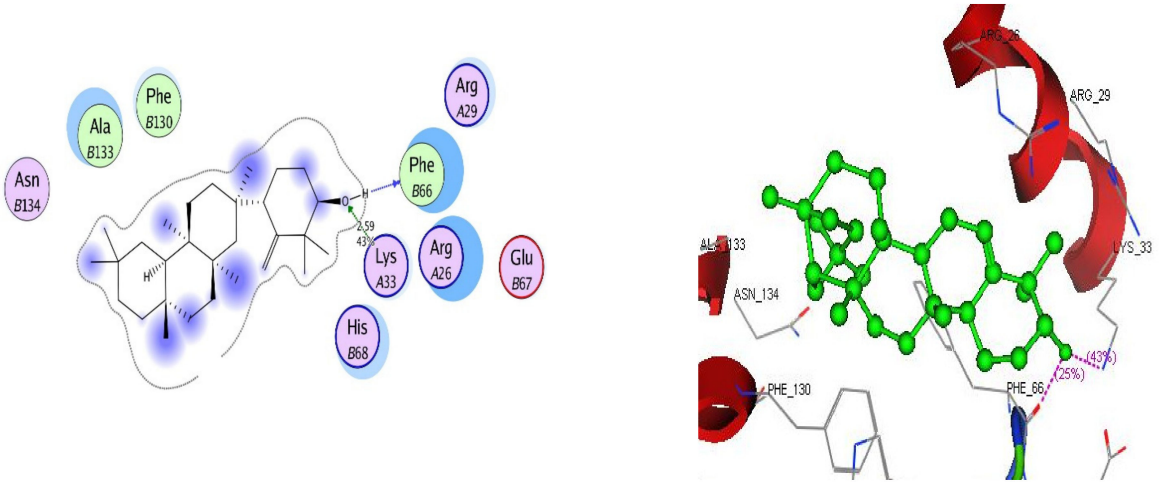
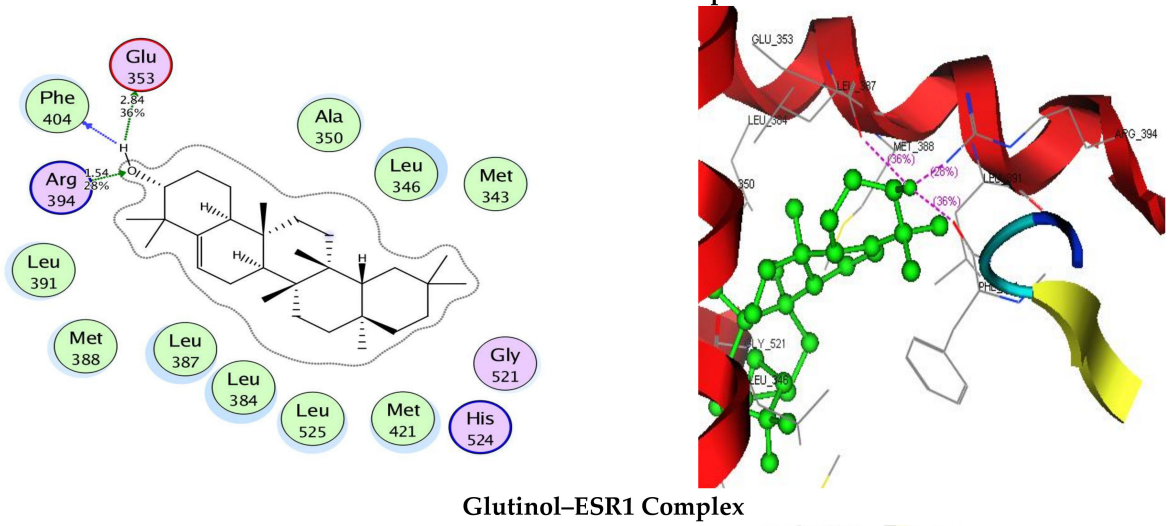


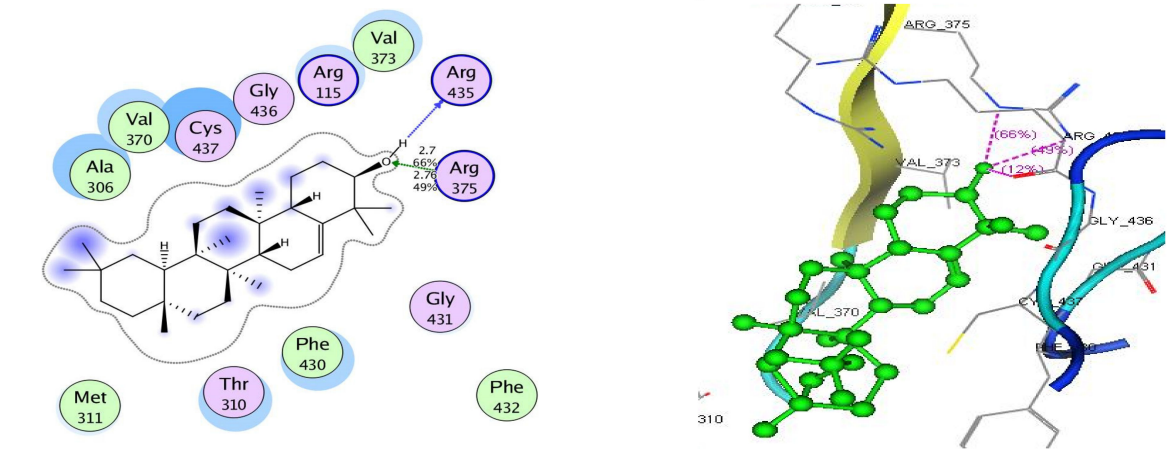
Figure 5. Glutinol-target-pathway network.



Glutinol–CCND1 Complex



Glutinol–ESR1 Complex



Glutinol–CYP19A1 Complex

Figure 6. *Cont.*

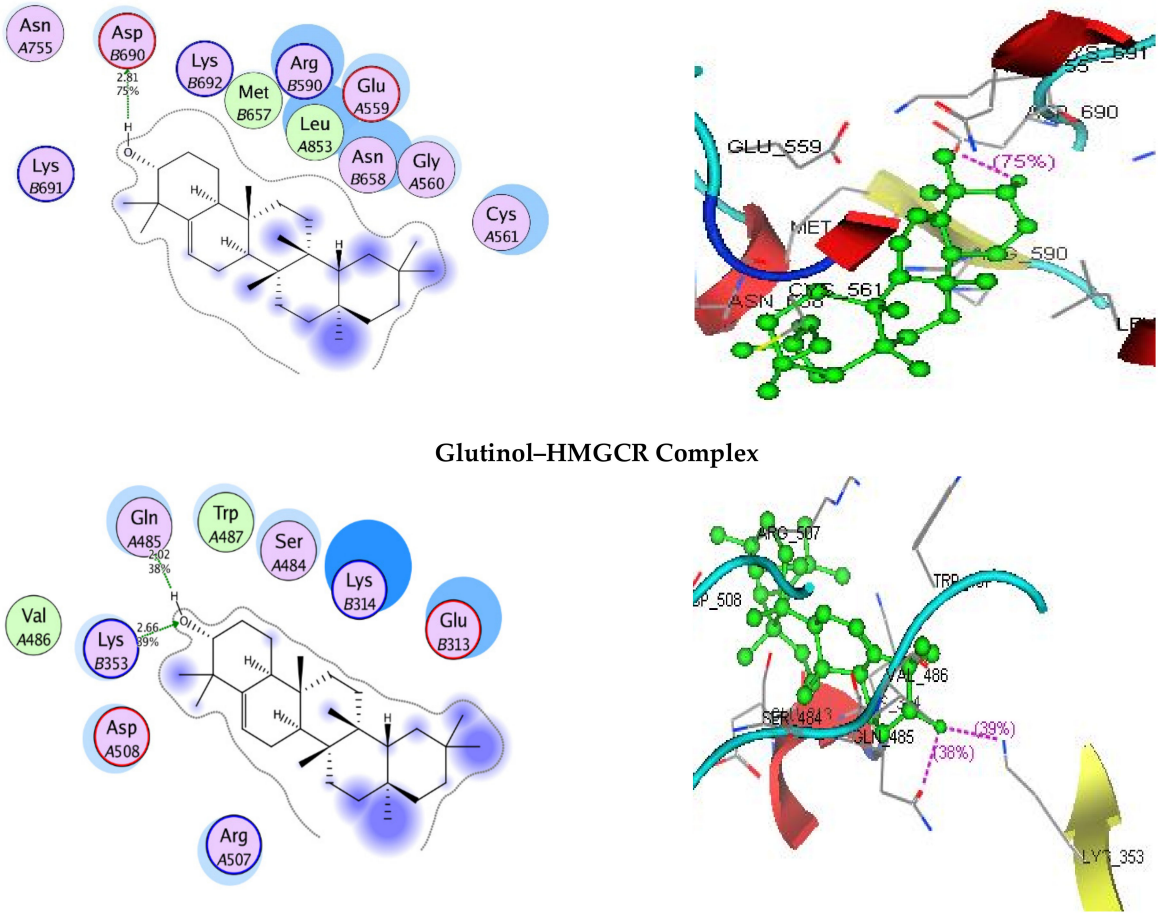


Figure 6. 3D and 2D images of best docked results A purple dotted line depicts metal or ion interaction, and a green dotted line depicts side-chain proton acceptor/donors. Basic and acidic amino acids are represented by blue and red circles, respectively. Certain amino acids have a blue backdrop because they have been exposed to solvents. Additionally, ligand atoms with blue coloring in front of them show solvent exposure.

Table 4. Glutinol-target molecular docking analysis.

Targets	Binding Energy (kJ/mol)	Interaction		
CCND1	−8.3554	2.59	43	LysA33
ESR1	−5.3991	2.84	36	Glu353
		1.54	28	Arg394
CYP19A1	−10.1795	2.7	66	Arg375
		2.76	50	Arg375
HMGCR	−5.9682	2.81	75	AspB690
PTPRC	−8.8985	2.02	38	GlnA485
		2.66	39	LysB353

4. Discussion

Currently, network pharmacology is receiving more and more attention during the medication development and utilization process [16]. This technique can, first and foremost, evaluate, screen, and optimize several key properties of medications in order to speed up or simplify the drug development process. This study not only identified some important biological features and genes potentially associated with glutinol using this network analysis method, but also included GO and KEGG enrichment analysis.

The development of a new drug is dependent not only on the drug's pharmacological effects, but also on its pharmacokinetic properties in terms of safety and availability in the body. The availability and toxicity profile of a lead molecule were anticipated using ADMET properties for test compounds. Predicted absorption metrics such as water solubility (log mol/L), skin permeability (log Kp), and intestinal solubility (percent absorbed) can be used in ADMET assessments to determine test compound therapeutic potential. According to certain investigations, substances with absorption properties have the ability to pass through the gut barrier and reach the target molecule via passive penetration. The results of the water solubility test demonstrated that glutinol is well absorbed. Furthermore, when compared to a reference value, the estimated intestinal solubility of the test drug showed good efficacy. When compared to a standard value (>30 percent abs), glutinol exhibited excellent intestinal solubility. Skin permeability ratings were also greater than the industry norm (−2.5 log Kp), indicating their utility as lead structures and demonstrating their drug-like action. Similarly, the permeability of the blood–brain barrier (BBB) and the central nervous system (CNS) of all screened substances was equal to standard values. According to many research reports, substances with a log BB value of more than 0.3 can cross the BBB, whereas those with a log BB value larger than −1 have poor brain penetration. Aside from these factors, the metabolic properties of test substances were investigated using the cytochrome P450 isoforms CYP3A4 and CYP1A2 [4]. The drug-likeness of glutinol was further supported by results for excretion and toxicity studies using total clearance (log mL/min/kg), LD50 values, maximum tolerated dose (MTD), and Ames toxicity.

The process of discovering new drugs necessitates finding target genes. Many genes and proteins have intricate connections with an increasing number of chemicals, substances, and medications [17]. Simultaneously, an increasing number of online analysis tools have been established in these investigations. BindingDB database research discovered 32 possible target genes connected to glutinol, as shown in Table 2. The 32 putative target genes were then examined using the STRING database. An important step in the drug discovery process is the hunt for target genes. The degrees of separation, betweenness centrality, and closeness centrality were all higher than the average of 3.85 nodes, the majority of which (such as CCND1, ESR1, CYP19A1, HMGCR, PTPRC, RELA, ELANE, and ITGAV) are involved in carcinogenesis and insulin resistance. At the same time, we used molecular docking to further investigate the probable interactions between glutinol and these targets. More likely, it will be that the ligand and receptor complex with a lower conformational energy confirms ligand stability. We found that the binding energy of 5 of the 8 targets was less than -5.0 kJmol^{-1}, indicating that glutinol may directly interact with these targets using a screening threshold of -5.0 kJmol^{-1}. As a result, glutinol's pharmacological activity could possibly be due to these targets.

We used the DAVID program to perform more GO and pathway analysis on these possible genes. Glutinol is linked to the steroid metabolic process, intracellular receptor signaling pathway, control of the inflammatory response, steroid biosynthesis, and organic hydroxyl compound biosynthesis, according to BP items. These findings suggest that glutinol has anti-inflammatory and anti-tumor properties. Chemical carcinogenesis-receptor activation and insulin resistance proved to be the most enriched pathways, according to KEGG pathway analysis. As a result, glutinol may have anti-cancer properties by primarily targeting AR, ITGAV, ESR1, ESR2, RELA, and VDR. Similarly, another study found that glutinol had anti-cancer properties, which is consistent with our GO and KEGG findings. The drug-target network diagram of glutinol, on the other hand, suggests that glutinol could have a broad range of pharmacological effects.

5. Conclusions

Our research revealed that glutinol has a wide range of pharmacological effects. At the same time, we looked into glutinol's likely mechanism of action, which could be exploited to produce more effective anticancer and anti-diabetic medications. Our findings offer a new perspective on glutinol research, development, and therapeutic application.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/pr10081492/s1.

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