

Research

Exploring the mechanisms of *Cornus officinalis* in the treatment of non-alcoholic steatohepatitis using network pharmacology, molecular docking and molecular dynamics simulations

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Abstract

Non-alcoholic steatohepatitis (NASH) is a predominant metabolic liver disease, typically characterized by hepatic steatosis, oxidative stress, and inflammation. The traditional Chinese medicine *Cornus officinalis* possesses anti-inflammatory and hepatoprotective pharmacological properties and has shown ameliorative effects on NASH. However, its mechanism of action remains unclear. This study aims to elucidate the mechanisms by which *C. officinalis* ameliorates NASH. The active components of *C. officinalis* were analyzed using the Traditional Chinese Medicine Systems Pharmacology Database (TCMSP), and the corresponding targets were predicted. Subsequently, the DisGeNET, GeneCards, and GEO databases were employed to identify NASH-related targets. Venn diagrams were used to intersect the *C. officinalis* targets with the NASH targets. Protein–protein interaction (PPI) networks were constructed using the STRING database, and PPI network analysis was performed using Cytoscape. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were conducted using the Database for Annotation, Visualization, and Integrated Discovery (DAVID), followed by molecular docking validation. *Cornus officinalis* was found to contain 20 major active ingredients corresponding to 672 potential targets, 61 of which overlapped with NASH targets. PPI network, GO, and KEGG pathway analyses identified four targets with the highest correlation, and molecular docking results indicated that the active ingredients of *C. officinalis* exhibited strong binding affinities to NASH targets. The treatment of NASH with *C. officinalis* is characterized by multiple active ingredients and multiple targets, underscoring the major advantage of traditional Chinese medicine in treating NASH.

Keywords *Cornus officinalis* · NASH · Network pharmacological · Molecular docking · Inflammation

1 Introduction

Non-alcoholic fatty liver disease (NAFLD) is a chronic disease caused by the accumulation of lipids in the liver, of which non-alcoholic steatohepatitis (NASH) is a manifestation [1]. NASH is a hepatic metabolic syndrome disorder caused by chronic liver injury and liver inflammation due to hepatic steatosis [2]. NASH is a progressive disease that

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usually leads to metabolic disorders and diabetes mellitus, and even progression to cirrhosis and hepatocellular carcinoma [3, 4]. With the improvement of living standards and the increase of high-fat food intake, the incidence of NASH in China has risen to 15%–30%, which is a very serious health threat [5]. Due to the complex pathogenesis of NASH, there is no effective therapeutic drugs have been found [6].

Traditional Chinese medicines (TCM) have multiple active ingredients that correspond to the complex pathogenesis of NASH, and there is growing evidence that TCM has a therapeutic effect on NASH [7–9]. *Cornus officinalis* is an herb of great medicinal value [10]. Pharmacological research has shown that *C. officinalis* has a variety of anti-inflammatory, antioxidant, anti-tumor and hepatoprotective effects [11]. For instance, Lin Wang et al. found that *C. officinalis* ameliorated autoimmune hepatitis by modulating oxidative stress and apoptosis [12]. However, NASH usually presents with hepatic steatosis, oxidative stress and inflammation [13]. Although *C. officinalis* has good anti-inflammatory and antioxidant effects, little research has been done on its ameliorative effects and pharmacological mechanisms in relation to NASH. Therefore, we have investigated the possible therapeutic effects and mechanisms of *C. officinalis* on NASH by means of network pharmacology and molecular docking, which may help to provide a direction for the treatment of clinical NASH.

Network pharmacology is a novel research methodology that uses database searches and computer simulations to predict possible mechanisms of action of drugs [14, 15]. In addition, combining network pharmacology and bioinformatics enables broader exploration of disease pathogenesis and drug pharmacological mechanisms of action [16]. In this research, we analyzed the active ingredients and target prediction of *Cornus officinalis*, and also predicted the possible targets for NASH development, identified the common targets of *C. officinalis* and NASH to find the most probable drug therapeutic target and active ingredient, and finally carried out the molecular docking validation. The active constituents and pharmacological mechanisms of *C. officinalis* were studied through network pharmacology, which may provide a direction for the future treatment of NASH in the clinic.

2 Materials and methods

2.1 Screening of active ingredients in *Cornus officinalis*

The Traditional Chinese Medicines Systematic Pharmacology (TCMSP, <https://tcmsp.com/tcmsp.php>) was used to identify the relevant active ingredients of *Cornus officinalis*, which were screened for bioavailability $\geq 30\%$ and drug-like properties ≥ 0.18 [17]. Compound structures were constructed using the ChemDraw software. Target prediction was then performed using the TCMSP and SwissTargetPrediction (<http://www.swisstargetprediction.ch/>) databases. Finally, gene name conversion was performed using the UniProt (<https://www.uniprot.org>) database.

2.2 NASH-related mechanistic targets

The DisGeNET (<http://www.disgenet.org/>), GeneCards (<https://www.genecards.org>), and GEO (<https://www.ncbi.nlm.nih.gov/geo/>) databases were used to find NASH-related targets, which were further analyzed by Venn diagrams.

2.3 Databases

GSE 147304 was selected for the GEO database, and gene expression was analyzed online using GEO2R, with differentially expressed genes having thresholds of $|\log_2FC| > 1$ and $P < 0.05$. Volcano plots were performed using R version 4.3.3.

2.4 *Cornus officinalis* active ingredient-target network

The active ingredient-target network of *C. officinalis* was generated using Cytoscape 3.7.1 software to show the intricate network relationship between active ingredients and targets for active ingredient screening.

2.5 Construction of protein–protein interaction networks (PPI)

The PPI network was obtained by importing the common targets of *C. officinalis* and NASH into the STRING (<https://www.string-db.org/>) database. Subsequently, the PPI data were imported into Cytoscape 3.7.1, and the core targets were analyzed by the NetworkAnalyzer tool. The PPIs were further analyzed using the cytoHubba and MCODE plugins.

2.6 GO and KEGG pathway enrichment analyses

GO and KEGG pathway enrichment analyses were performed using the *Cornus officinalis*-NASH common target genes in the DAVID database (<https://david.ncifcrf.gov/>). “Homo sapiens” was selected for GO analysis in terms of biological process (BP), molecular function (MF), and cellular component (CC), and 20 KEGG pathways associated with NASH were selected, then visualized using the Weishengxin platform (<https://www.bioinformatics.com.cn/>).

2.7 Construction of pathway-target networks

The top 10 NASH-associated signaling pathways, sorted by gene ratio, and common targets were selected for pathway-target network analysis. Key signaling pathways and targets were then identified.

2.8 Molecular docking validation

Molecular docking was performed to validate the key active components of *C. officinalis* with screened NASH core targets. The MOL2 files of the key active ingredients of *C. officinalis* were downloaded from TCMSP, and the protein structures were obtained from PDB (<http://www.rcsb.org/>) and saved in PDB format. We searched the PDB Protein Structure Database for 3D structures of key proteins and selected proteins with high resolution and long structures in the human background. The target proteins and small molecules were then processed to remove water, add hydrogen, add charge and set rotatable bonds. Grids were used to represent the active sites of proteins. The identification of active pocket sites covered the entire protein structure to facilitate comprehensive ligand binding across the entirety of the protein surface, and grid files describing the active sites were generated using the AutoGrid program. Finally, AutoDock was used for molecular docking.

2.9 Molecular dynamics simulation

Molecular dynamics simulations were performed using GROMACS software. Before simulation, the protein structure was pre-processed to eliminate crystalline water molecules and heteroatoms. Coordinates and parameters for active compounds were obtained from the CHARMM36 force field. Energy minimization and equilibrium simulations were performed to bring the system to a steady state. The simulation cassette was filled with TIP3P water model and the protein was placed in the center of the cassette at a distance of 1.0 nm from the cassette boundary. The system was equilibrated with the canonical ensemble (NVT) and isothermal isobaric ensemble (NPT) sets for 100 ps. The equilibrated system was configured to maintain a temperature of 310 K and a standard pressure of 1.0 bar. After 100 ns of simulation, root mean square of deviation (RMSD), root mean square of fluctuation (RMSF), radius of gyration (RG) and hydrogen bonding interactions were evaluated.

3 Results

3.1 Active components of *Cornus officinalis*

We retrieved a total of 226 active ingredients of *C. officinalis* in TCMSP, of which 20 active ingredients met the criteria of oral bioavailability (OB) $\geq 30\%$ and drug-like properties ≥ 0.18 (Table 1).

3.2 *Cornus officinalis* targets

We searched the TCMSP and SwissTargetPrediction databases and obtained 672 target genes corresponding to the active components of *C. officinalis* after removing duplicates (Fig. 1).

Table 1 Active ingredients of *Cornus officinalis*

Molecule ID	Molecule Name	PubChem CID	OB (%)	DL
MOL001494	Mandenol	5,282,184	42	0.19
MOL001495	Ethyl linolenate	5,367,460	46.1	0.2
MOL001771	poriferast-5-en-3beta-ol	457,801	36.91	0.75
MOL002879	Diop	33,934	43.59	0.39
MOL002883	Ethyl oleate (NF)	5,363,269	32.4	0.19
MOL003137	Leucanthoside	442,659	32.12	0.78
MOL000358	beta-sitosterol	222,284	36.91	0.75
MOL000359	sitosterol	222,284	36.91	0.75
MOL000449	Stigmasterol	5,280,794	43.83	0.76
MOL005360	malkangunin	90,473,155	57.71	0.63
MOL005481	2,6,10,14,18-pentamethylicosa-2,6,10,14,18-pentaene	5,366,013	33.4	0.24
MOL005486	3,4-Dehydrolycopen-16-al	5,316,458	46.64	0.49
MOL005489	3,6-Digalloylglucose	6,398,541	31.42	0.66
MOL005503	Cornudentanone	442,735	39.66	0.33
MOL005530	Hydroxygenkwanin	5,318,214	36.47	0.27
MOL005531	Telocinobufagin	259,991	69.99	0.79
MOL008457	Tetrahydroalstonine	72,340	32.42	0.81
MOL000554	gallic acid-3-O-(6'-O-galloyl)-glucoside	11,972,353	30.25	0.67
MOL005552	gemin D	471,119	68.83	0.56
MOL005557	lanosta-8,24-dien-3-ol,3-acetate	11,190,577	44.3	0.82

3.3 *Cornus officinalis*-NASH common targets

The GSE147304 gene chip was obtained from the GEO database, and 249 differentially expressed genes were screened (Fig. 2A). In addition, 434 and 3935 NASH possible targets were found in DisGeNET and GeneCards, respectively. We found 299 genes in multiple databases as NASH targets (Fig. 2B). Finally, we overlapped the screened *C. officinalis* targets with NASH targets and identified 61 *Cornus officinalis*-NASH common targets (Fig. 2C).

3.4 Construction and analysis of PPI network

We imported the 61 targets into the STRING database for PPI network analysis. Then, the PPI network data were uploaded to Cytoscape and analyzed using three parameters: betweenness centrality, closeness centrality, and node degree, where the larger the parameter value, the more critical the node is (Fig. 3A). We show here the top 20 nodes sorted by degree

Fig. 1 *Cornus officinalis* active ingredients and targets. Green and blue colors represent *C. officinalis* targets predicted by TCMSP and SwissTargetPrediction

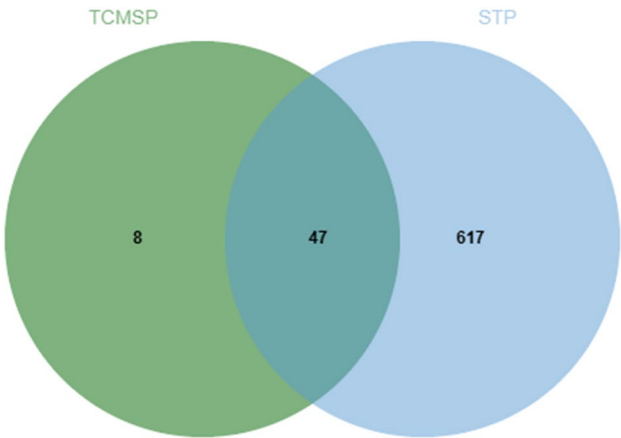
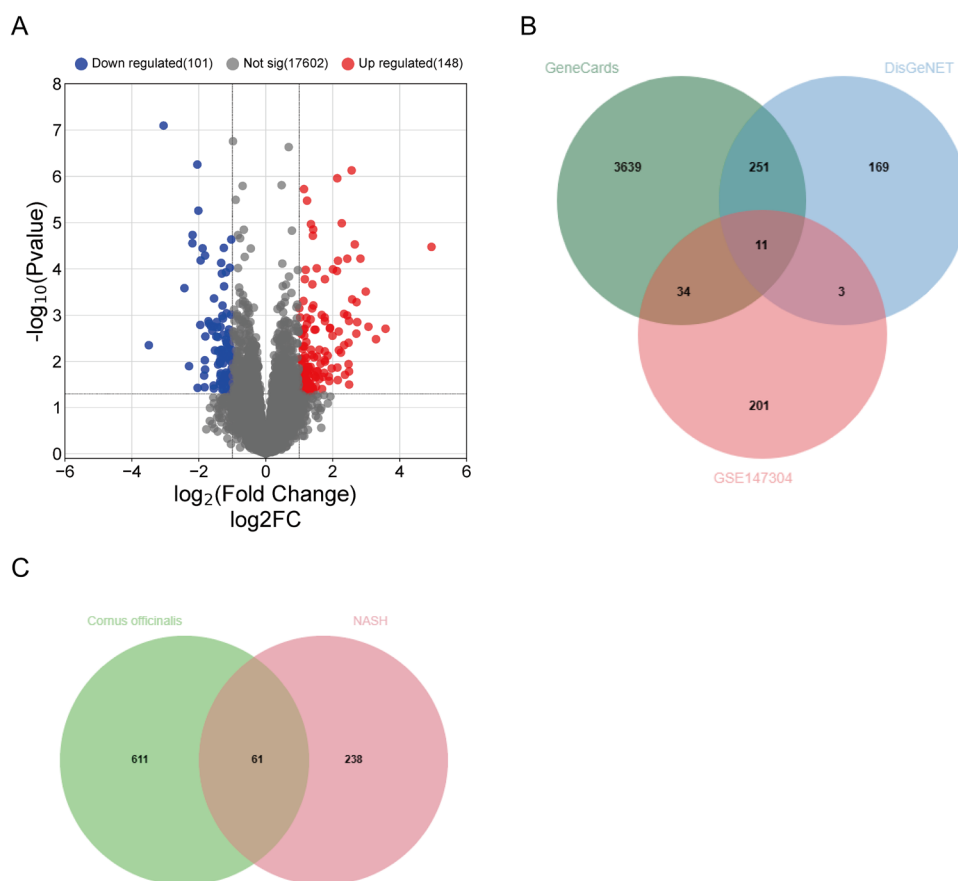


Fig. 2 *Cornus officinalis* and NASH common targets. **A** Differential gene volcano map for normal and NASH samples of the GSE147304 dataset. **B** DisGeNET, GeneCards and GSE14703 datasets NASH-related gene Venn diagrams. **C** Venn diagram of the *C. officinalis* -NASH common target



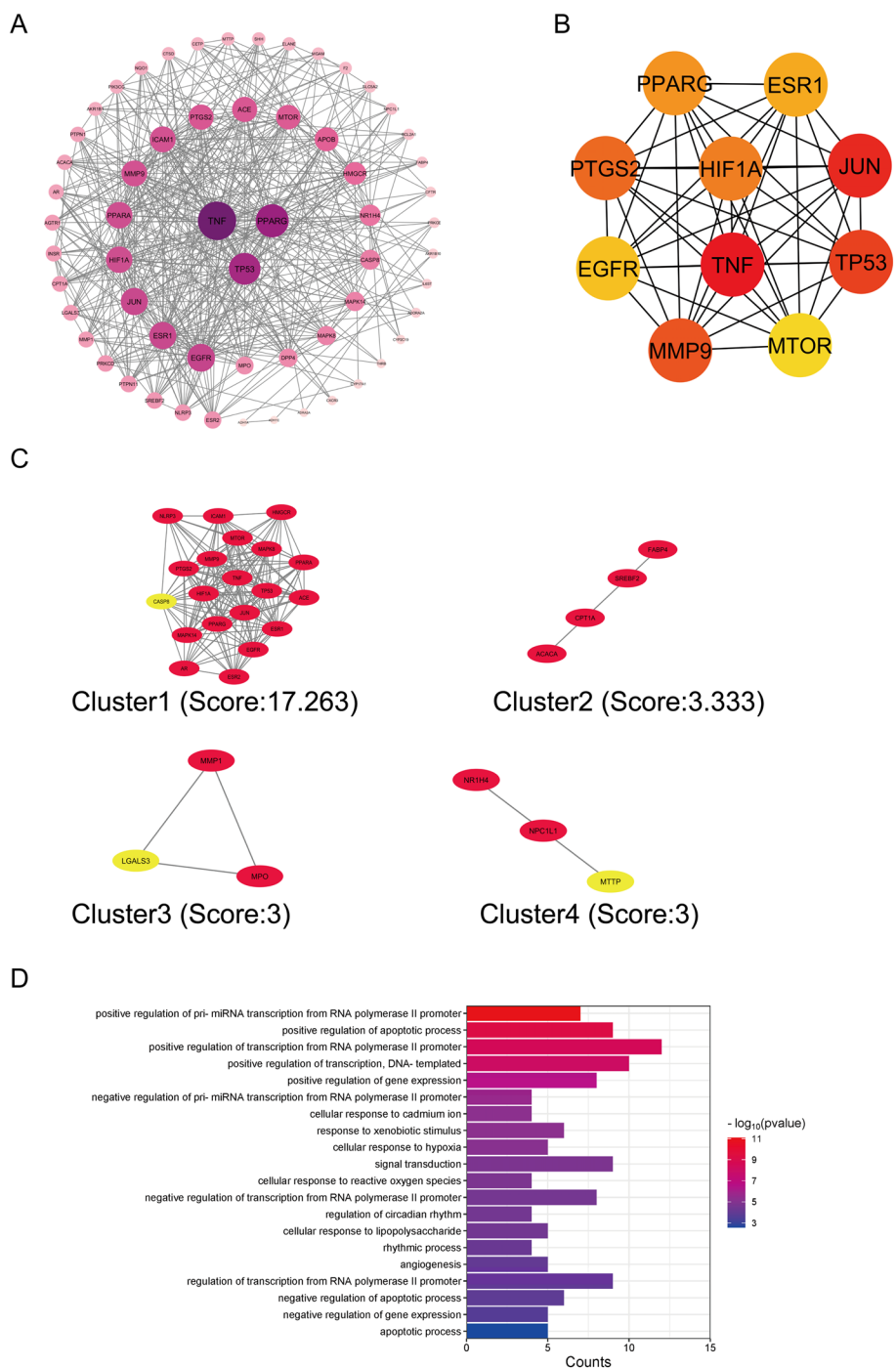
value (Table 2). The MCC algorithm of cytoHubba showed that the top ten genes include PPARG, ESR1, JUN, TP53, MTOR, MMP9, EGFR, PTGS2, HIF1A, and TNF (Fig. 3B). In addition, through MCODE plugin analysis, the 61 target targets were divided into four protein clusters. These targets were mainly concentrated in Cluster 1 with CASP5 as the seed (Fig. 3C). Next, we mainly analyzed the biological processes (BP) in the GO terms of Cluster 1, and found that they were mainly concentrated in processes such as positive regulation of transcription from RNA polymerase II promoter and positive regulation of transcription, and DNA-templated (Fig. 3D).

3.5 GO and KEGG Pathway enrichment analyses

We performed GO and KEGG enrichment analyses of the 61 *Cornus officinalis*-NASH common targets using the DAVID database. GO enrichment analyses showed that the enriched biological processes (BP) included positive regulation of transcription from RNA polymerase II promoter and negative regulation of apoptotic process. Enriched cellular components (CC) included plasma membrane, cytosol, and cytoplasm. Enriched molecular functions (MF) included protein binding and enzyme binding (Fig. 4A).

KEGG analysis revealed a total of 95 enriched pathways. The top twenty NASH-related pathways were selected for analysis. These enriched pathways mainly included Insulin resistance, Lipid and atherosclerosis, IL-17 signaling pathway, and TNF signaling pathway (Fig. 4B). Categorizing the 20 pathways enriched by KEGG, the pathways were classified into metabolism (lipid metabolism), organismal systems (immune system, endocrine system, sensory system, and digestive system), human diseases (endocrine and metabolic diseases and cardiovascular diseases), and signal transduction (TNF signaling pathway, AMPK signaling pathway, MAPK signaling pathway, NF-kappa B signaling pathway, HIF-1 signaling pathway, FoxO signaling pathway, cAMP signaling pathway, and JAK-STAT signaling pathway) (Fig. 4C, D).

Fig. 3 *Cornus officinalis* and NASH common targets PPI network. **A** PPI network of *C. officinalis* -NASH common targets analyzed by Cytoscape topological parameters. **B** The top 10 hub genes. **C** Four protein clusters obtained by MCODE analysis (The yellow color represents the seed gene). **D** GO-BP analysis of protein cluster 1



3.6 Target-pathway network analyses

To further explore the relationship between targets and pathways, the 20 enriched pathways were analyzed as the top 10 by gene ratio for chordal graph analysis. In addition, the target-pathway network was constructed and analyzed by the NetworkAnalyzer tool. This analysis revealed that the core targets of the KEGG pathway included MAPK8, TNF, JUN, MTOR, INSR, and MAKP14 (Fig. 5).

Table 2 Top 20 targets in terms of degree value

Targets	Betweenness	Closeness	Degree	Targets	Betweenness	Closeness	Degree
TNF	0.14675618	0.81944444	48	PTGS2	0.02517777	0.64130435	28
PPARG	0.07491026	0.7375	40	ACE	0.04779716	0.64130435	28
TP53	0.05185556	0.7195122	38	MTOR	0.01501648	0.6344086	27
EGFR	0.03740858	0.64835165	32	APOB	0.03032769	0.62765957	26
ESR1	0.03771091	0.64130435	31	HMGCR	0.03012056	0.61458333	24
JUN	0.02059455	0.66292135	31	NR1H4	0.02833634	0.5959596	22
HIF1A	0.02208565	0.65555556	30	CASP8	0.00467896	0.57281553	20
PPARA	0.0342334	0.65555556	30	MAPK8	0.00512422	0.56730769	19
MMP9	0.02145867	0.64835165	29	MAPK14	0.00275219	0.56730769	19
ICAM1	0.02429173	0.62765957	29	DPP4	0.01290561	0.57281553	18

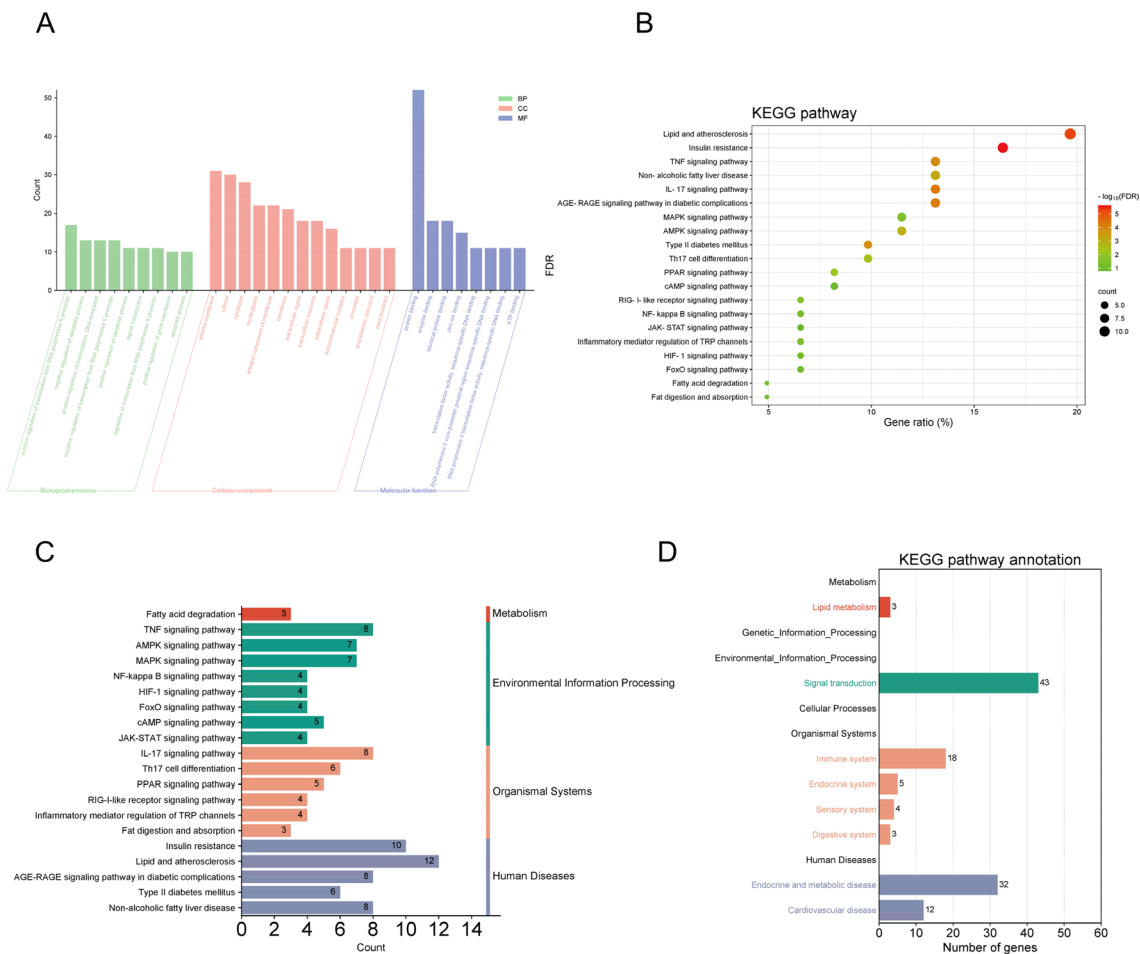


Fig. 4 GO and KEGG Pathway enrichment analyses. **A** Top 30 GO terms by gene ratio. (BP stands for biological process; CC stands for cellular component; MF stands for molecular function.) **B** Bubble map of NASH-associated pathways of 20 KEGG enrichment. **C** and **D** show the pathway classification analysis of KEGG enrichment

3.7 Molecular docking verification

Based on the above analysis, we selected five core components (Leucanthoside, Ethyl linolenate, Diop, poriferast-5-en-3beta-ol, and Mandenol) and four core targets, including TNF, JUN, MTOR, and PPARG for molecular docking

Fig. 5 Target–Pathway network. Diagram of the *C. officinalis* target-pathway network. (The larger nodes represent higher degree values.)

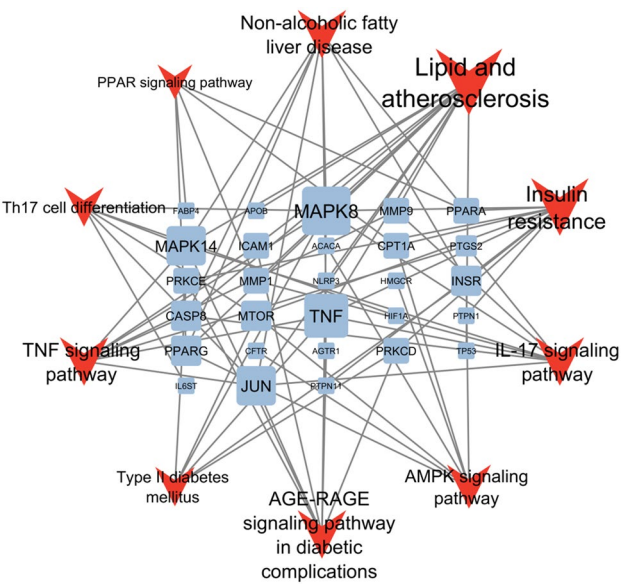


Table 3 Key active ingredients of *Cornus officinalis*

Molecule ID	Molecule Name	PubChem CID	OB (%)	DL	Structure
MOL003137	Leucanthoside	442,659	32.12	0.78	
bMOL001495	Ethyl linolenate	5,367,460	46.1	0.2	
MOL002879	Diop	33,934	43.59	0.39	
MOL001771	poriferast-5-en-3beta-ol	457,801	36.91	0.75	
MOL001494	Mandenol	5,282,184	42	0.19	

Table 4 Core targets of *Cornus officinalis*

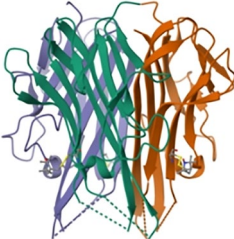
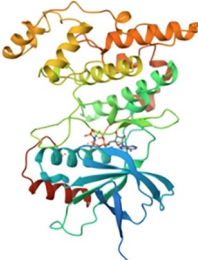
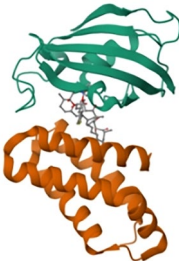
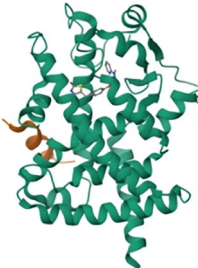
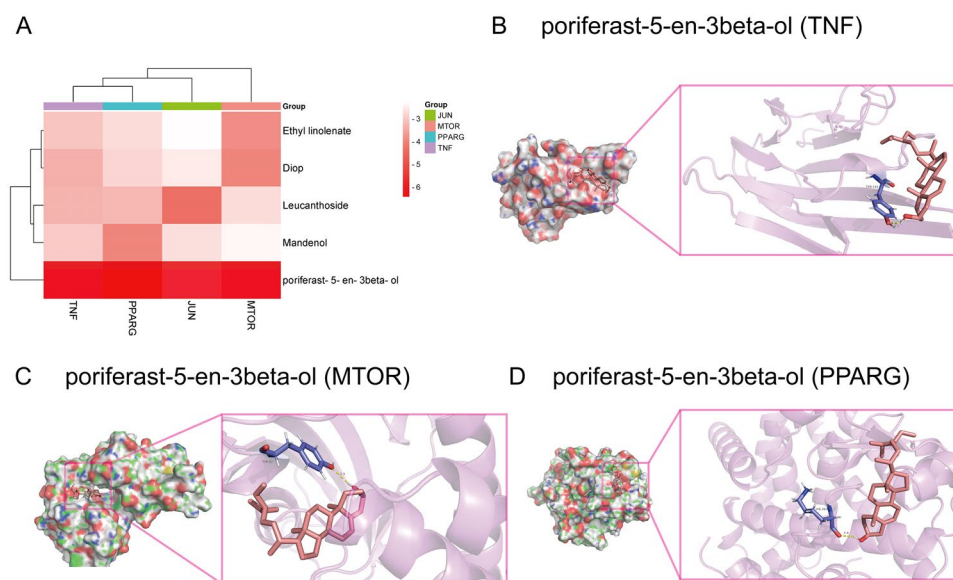
Protein	PDB ID	Structure
TNF	5uui	
JUN	1jnk	
MTOR	3fap	
PPARG	1zgy	

Table 5 Binding affinities between active components and core targets of *Cornus officinalis*

Compound	Docking Score (kcal/mol)			
	TNF	JUN	MTOR	PPARG
Leucanthoside	−3.31	−4.3	−2.73	−3.24
Ethyl linolenate	−3.07	−2.25	−3.87	−2.73
Diop	−3.35	−2.53	−4	−2.8
poriferast-5-en-3beta-ol	−6	−5.62	−6.03	−6.42
Mandenol	−3	−2.68	−2.36	−4

(Tables 3 and 4). It was found that poriferast-5-en-3beta-ol docked more favorably with TNF (−6 kcal/mol), MTOR (−6.03 kcal/mol), and PPARG (−6.42 kcal/mol) (Table 5, Fig. 6).

Fig. 6 Molecular docking of *C. officinalis* with potential NASH targets. **A** Heat map of molecular docking of active ingredient and target. Visualization of poriferast-5-en-3beta-ol docking with TNF (**B**), MTOR (**C**), and PPARG (**D**)



3.8 Molecular dynamics simulation

To further investigate the stability of protein–ligand complexes, molecular dynamics simulations were performed. Root mean square deviation (RMSD) analysis showed that TNF-poriferast-5-en-3beta-ol and PPARG-poriferast-5-en-3beta-ol were stable after 80 ns and 40 ns, respectively (Fig. 7A). RMSF analysis of residue fluctuations in the ligand–protein complex revealed that TNF-poriferast-5-en-3beta-ol fluctuates more at 90, while PPARG-poriferast-5-en-3beta-ol fluctuates the most at 270 (Fig. 7B). The radius of gyration (RG) results also showed that TNF-poriferast-5-en-3beta-ol and PPARG-poriferast-5-en-3beta-ol have a more stable radius of gyration, implying that the protein conformation is stable (Fig. 7C). The number of hydrogen bonds also demonstrated a better binding of the protein ligands (Fig. 7D). While MTOR-poriferast-5-en-3beta-ol showed static stability, it exhibited instability in a dynamic environment as observed from kinetic analysis (Fig. 7E–H).

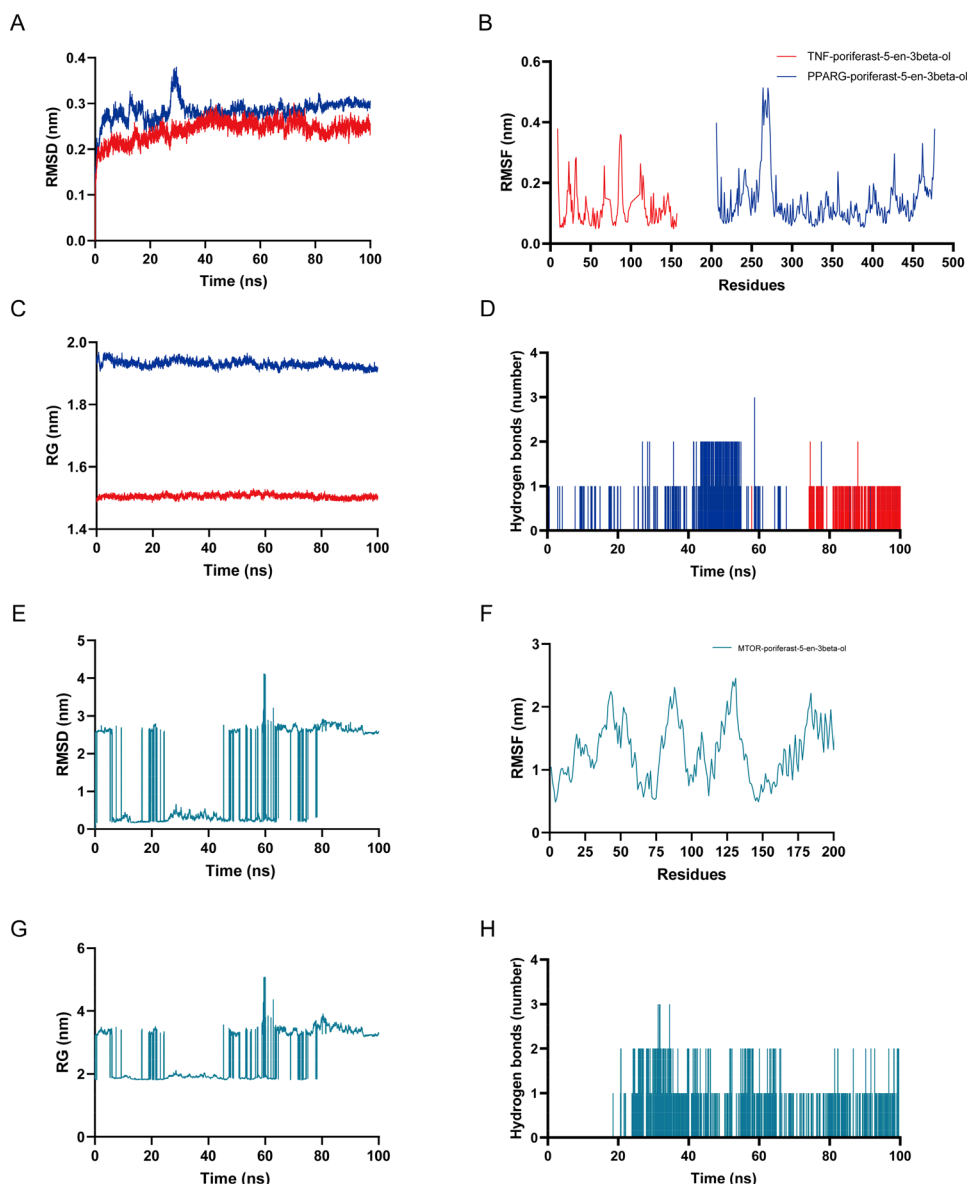
4 Discussion

Non-alcoholic steatohepatitis (NASH) is a more severe subtype of NAFLD, and people with NASH are more likely to develop diseases such as cirrhosis and liver cancer [13, 18]. There is now a large body of evidence confirming the ameliorative effects of herbal active ingredients on NASH [19]. The traditional herb *C. officinalis* has been documented to have antioxidant, anti-apoptotic and anti-tumor properties [20]. In this research, we predicted the possible targets of *C. officinalis* for the treatment of NASH by a network pharmacology approach and validated them by molecular docking.

Pharmacological and non-pharmacological interventions for NASH have been extensively researched. Current pharmacological treatments include pioglitazone, vitamin E, and obeticholic acid, which primarily target insulin resistance, oxidative stress, and bile acid metabolism, respectively [21]. Non-pharmacological interventions, such as lifestyle changes involving diet and exercise, are also critical for managing NASH [22]. Our study contributes to this body of knowledge by highlighting the potential of *Cornus officinalis*, a traditional herb with multi-targeted actions. The unique advantage of *C. officinalis* lies in its polypharmacology, targeting multiple pathways simultaneously, which may offer a more holistic approach to managing NASH compared to single-target drugs.

Our results showed that the KEGG pathway were enriched mainly in lipid and atherosclerosis, Insulin resistance, TNF signaling pathway and AMPK signaling pathway. NASH is a manifestation of hepatic metabolic disorders, usually in the form of hepatic steatosis, insulin resistance, hepatic inflammation and oxidative stress [23]. TNF- α signaling can further promote NF- κ B expression, leading to a vicious cycle of inflammation [24]. There has been much evidence that

Fig. 7 Molecular dynamics simulations of protein–ligand complexes. **A** Root mean square deviation analysis of TNF-poriferast-5-en-3beta-ol and PPARG-poriferast-5-en-3beta-ol. **B** RMSF profiles of amino acid residues during molecular dynamics simulations of TNF-poriferast-5-en-3beta-ol and PPARG-poriferast-5-en-3beta-ol. **C** RG profiles of proteins during molecular dynamics simulations of TNF-poriferast-5-en-3beta-ol and PPARG-poriferast-5-en-3beta-ol. **D** Hydrogen bonding interactions between TNF-poriferast-5-en-3beta-ol and PPARG-poriferast-5-en-3beta-ol. **E** Root mean square deviation analysis of MTOR-poriferast-5-en-3beta-ol. **F** RMSF profiles of amino acid residues during molecular dynamics simulations of MTOR-poriferast-5-en-3beta-ol. **G** RG profiles of proteins during molecular dynamics simulations of MTOR-poriferast-5-en-3beta-ol. **H** Hydrogen bonding interactions between MTOR-poriferast-5-en-3beta-ol



the adenosine 5'-monophosphate (AMP) activated protein kinase (AMPK) signaling cascade in hepatocytes has an impact on metabolic dysregulation [25]. AMPK and mTOR-related pathways are key proteins regulating hepatic lipid and glucose metabolism [26]. In conjunction with our research, it can be hypothesized that the active components of *C. officinalis* may play a therapeutic role in NASH by modulating these NASH-related signal pathways.

Through analysis, we identified the most critical targets of *C. officinalis* for the treatment of NASH including TNF, PPARG, MTOR and JUN. TNF- α is an adipocytokine that is critical in lipid and insulin regulation [27]. At the same time, TNF- α is a pro-inflammatory cytokine associated with both non-immune and immune cells, triggering an inflammatory response [28]. Peroxisome proliferator-activated receptor gamma (PPAR γ), one of the nuclear hormone receptors, plays an important role in lipid metabolism and inflammatory response [29]. PPAR γ activation promotes adipogenesis and lipid uptake in adipocytes, leading to lipid accumulation, which is critical for NASH [30]. Mammalian target of rapamycin (mTOR) signaling affects lipid metabolism, protein synthesis, and cell growth by interacting with specific splice proteins [31]. At Present, mTOR has been shown to regulate hepatic inflammation, oxidative stress and autophagy [32]. Research has shown that c-Jun N-terminal kinase (JNK) activation induces lipotoxic injury, leading to mitochondrial dysfunction and oxidative stress, which are critical in the development of NASH [33, 34]. The above analysis demonstrated that the possible targets we screened for the treatment of NASH with *C. officinalis* have great therapeutic potential.

Combining the results of network pharmacology and molecular docking, we identified one of the most effective active components (poriferast-5-en-3 β -ol) in the treatment of NASH by *Cornus officinalis*. Poriferast-5-en-3 β -ol also known as γ -sitosterol is one of the phytosterols [35]. Phytosterols are steroids synthesized by plants, and it has been reported in research that the intake of foods rich in phytosterols can reduce the risk of cancer [36]. As a common phytosterol, β -sitosterol has pharmacological effects such as anti-inflammatory, antioxidant and antidiabetic. β -sitosterol has been researched and found to have an ameliorative effect on NASH [37]. In contrast to γ -sitosterol, which has been more sparsely researched. The present research, validated by network pharmacology and molecular docking, hypothesized that γ -sitosterol is most likely to be the most important active ingredient in the treatment of NASH by *Cornus officinalis*.

Using publicly available databases such as the GEO dataset has potential limitations, including missing or incomplete information. Consequently, the use of this data for research purposes does not pose any ethical issues. We will provide the raw data used in our analysis as supplementary material or deposit it in a public repository to enhance reproducibility.

Overall, *C. officinalis* have potential as traditional Chinese medicine for the treatment of NASH. Finding active ingredients and targets through a network pharmacology approach may also facilitate modification of drug structures to improve efficacy. The drawback of this research is that there are only theoretical speculations on the pharmacological effects of *Cornus officinalis*. Therefore, further experimental validation of the analyzed results is needed, which will be of great interest for clinical NASH treatment. This includes testing the active components of *C. officinalis* in cell culture models of NASH and animal models to confirm their therapeutic effects. Clinical trials are also necessary to evaluate the safety and efficacy of *C. officinalis* in NASH patients. The potential clinical implications include further research on the safety and efficacy of *C. officinalis* in NASH patients and the potential for combining it with other therapies. Moreover, there is a need to address the limitations of each computational method used and the challenges in translating the findings to clinical practice.

5 Conclusion

Research has shown that the active ingredients of *C. officinalis* ameliorate NASH by affecting insulin and lipid metabolism, hepatic inflammation, and oxidative stress mainly through the lipid and atherosclerosis, Insulin resistance, TNF signaling pathway and AMPK signaling pathway. Molecular docking has shown that the active ingredients of *C. officinalis* interact directly with a variety of NASH-related proteins, most centrally with TNF, JUN, MTOR, and PPARG. These results suggest that *C. officinalis* may have great potential for the treatment of NASH.

Author contribution Conceptualization, JG; methodology, JG; software, JG; validation, JW; formal analysis, JG; investigation, JG; resources, TW; data curation, JW; writing original draft preparation, JG; writing review and editing, JG and JW; visualization, TW; supervision, TW; project administration, JW; funding acquisition, TW. All authors have read and agreed to the published version of the manuscript.

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Data availability All data obtained in this paper by analyzing this research are available from the authors.

Declarations

Competing interests The authors have no relevant competing interests to declare.

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