



Original Article



Verify the Therapeutic Effect of Effective Components of *Lycium Barbarum* on Hepatocellular Carcinoma Based on Molecular Docking

Mengxiao Liu¹ , Ji Li¹ , Kui Yu¹ , Qian Yu² and Shuying Li^{1*}

¹School of Basic Medical Sciences, Hebei Key Laboratory for Chronic Diseases, North China University of Science and Technology, Tangshan, Hebei, China; ²Tangshan Hospital of Traditional Chinese Medicine, Tangshan, Hebei, China

Received: January 21, 2025 | Revised: March 05, 2025 | Accepted: March 19, 2025 | Published online: March 31, 2025

Abstract

Background and objectives: In recent years, it has been found that *Lycium barbarum* can repair liver damage and promote liver regeneration. Additionally, the polysaccharides contained in *Lycium barbarum* have anticancer properties and can induce apoptosis in cancer cells. Molecular docking, a mature computer-aided method, is widely used in drug discovery. This study aimed to verify the efficacy of active ingredients of *Lycium barbarum* in the treatment of liver cancer by molecular docking.

Methods: The effect of the active ingredients of *Lycium barbarum* in the treatment of liver cancer was verified by molecular docking, based on a previous study that examined the impact of *Lycium barbarum* on liver cancer using network pharmacology.

Results: The binding energies of the key active ingredients and core targets were all less than -5.0 kcal/mol ($1 \text{ kcal} = 4.184 \text{ J}$), with most of them being less than -7.0 kcal/mol. This indicates that the key active ingredients and core targets have good binding ability, with most demonstrating strong binding affinity.

Conclusions: Most of the active ingredients in wolfberry can spontaneously bind to the core target protein, thereby playing a therapeutic role in liver cancer.

Introduction

Liver cancer is one of the malignant tumors that seriously threatens human health worldwide. Approximately 865,269 new cases are reported each year, accounting for 4.3% of all malignant tumors. About 757,948 people die from liver cancer annually, which accounts for 7.8% of all cancer-related deaths.¹ Studies have shown that the active ingredients of wolfberry have a positive effect on anti-liver cancer, cervical cancer, gastric cancer, etc., and have become valuable natural compounds for the treatment or adjunctive treatment of these tumors.^{2–4} Wolfberry extracts can regulate pathophysiological processes such as inflammatory responses, lipid metabolism, liver fibrosis, and tumor occurrence and development through various signal

transduction pathways, alleviating the symptoms of various liver diseases.^{5,6} Among these, *Lycium barbarum* polysaccharides can significantly prevent alcohol-induced hepatotoxicity through the antioxidant and anti-apoptotic activities of the Nrf2 signaling pathway in a dose-dependent manner.⁷ The use and application of molecular docking in drug discovery have changed significantly over the past few years. It enables the discovery of potential therapeutic drugs based on computer-structured approaches, the identification of novel therapeutic compounds, the prediction of ligand-target interactions at the molecular level, and the characterization of structure-activity relationships without prior knowledge of the chemical structures of other target modulators.⁸ In this study, based on the preliminary network pharmacological analysis of the active ingredients of *Lycium barbarum* in the treatment of liver cancer, molecular docking was conducted to verify the active ingredients' role in the treatment of liver cancer, providing a theoretical basis for clinical liver cancer treatment.

Keywords: Network pharmacology; Molecular docking; Active ingredients; *Lycium barbarum*; Therapeutic; Liver cancer.

*Correspondence to: Shuying Li, School of Basic Medical Sciences, Hebei Key Laboratory for Chronic Diseases, North China University of Science and Technology, Tangshan, Hebei 063210, China. ORCID: <https://orcid.org/0000-0001-9781-2336>. Tel: +86-0315-8805515, E-mail: lisy5001@sina.com

How to cite this article: Liu M, Li J, Yu K, Yu Q, Li S. Verify the Therapeutic Effect of Effective Components of *Lycium Barbarum* on Hepatocellular Carcinoma Based on Molecular Docking. *Oncol Adv* 2025;000(000):000–000. doi: 10.14218/OnA.2025.00003.

Materials and methods

Active ingredient screening and preliminary treatment

The role of the active ingredients of *Lycium barbarum* in the treat-

Table 1. The top 10 active ingredients of wolfberry screened in this study

Mol ID	Molecule name	OB (%)	DL
MOL010234	delta-Carotene	31.8	0.55
MOL009678	lanost-8-enol	34.23	0.74
MOL009677	lanost-8-en-3beta-ol	34.23	0.74
MOL009604	14b-pregnane	34.78	0.34
MOL000358	beta-sitosterol	36.91	0.75
MOL008173	daucosterol	36.91	0.75
MOL009617	24-ethylcholest-22-enol	37.09	0.75
MOL009615	24-Methylenecycloartan-3beta,21-diol	37.32	0.8
MOL005438	Campesterol	37.58	0.71
MOL009635	24-methyllophenol	37.83	0.75

DL, drug-like; OB, oral bioavailability.

ment of liver cancer was discussed based on a previous network pharmacology study.⁹ The effective active ingredients of *Lycium barbarum* in the treatment of liver cancer and the intersection targets of liver cancer in various databases were obtained and displayed using a Venn diagram. The selected key targets (intersection targets) were uploaded to the STRING database (<https://cn.string-db.org>), and the function “Multiple proteins” was selected to predict the protein interaction network. The species were limited to Homo sapiens, and the interaction confidence threshold was set to medium (≥ 0.400). Finally, the generated protein-protein interaction (PPI) network data were imported into Cytoscape 3.9.1 for visual analysis. Key targets were analyzed through gene ontology (GO) function annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis ($P < 0.01$), and the potential mechanism of *Lycium barbarum* against liver cancer was illustrated using a bubble chart/bar chart from the Weshengxin platform.

Molecular docking

The role of the active ingredients of *Lycium barbarum* in the treatment of liver cancer was verified by molecular docking. The core targets of the core prescription, ranked in the top seven based on degree value from high to low, were interlinked with the selected key active ingredients. The 3D structure of the active ingredients was downloaded from the TCMSP database and obtained from the PDB (<http://www.rcsb.org/>) database, and the structure of the core target protein was retrieved. PyMOL software was used for the initial treatment of the core target, such as hydrogenation, deletion of water molecules, and small molecule ligands. The three-dimensional structures of key active ingredients and core target proteins were converted into appropriate formats using AutoDock Tools and Open Babel. Molecular docking was verified using AutoDock Vin. The binding activity of key active ingredients and core targets was evaluated by binding energy, and the conformation with the most stable binding was selected. Finally, the results were processed on the PLIP website, and the molecular docking results were visualized using PyMOL software.

Results

Acquisition of effective active ingredients

Forty-five active ingredients with MOLID numbers were obtained

through screening conditions “drug-like ≥ 0.18 ” and “oral bio-availability $\geq 30\%$ ”, among which the top 10 key active ingredients in the “Chinese Medicine-active ingredient-target-disease” PPI network were δ -carotene, lano-8-enol, lano-8-ene-3beta-ol, 14b-pregnane, β -sitosterol, carotenin, 24-ethylcholester-22-enol, 24-methylene cycloanthrane-3beta, 21-diol, canolasterol, and 24-methyllophenol (see Table 1).⁹ Their structures are shown in Figure 1. A total of 272 liver cancer intersection targets from each database was obtained, as shown in Figure 2. The top seven core targets in the PPI network include AKT1, TNF, EGFR, ESR1, SRC, PPARG, and HSP90AA1. The core targets were visualized and screened using Cytoscape, as shown in Figure 3. The KEGG enrichment results were sorted according to count value, and the top 10 signaling pathways for *Lycium barbarum* therapy for liver cancer were identified. A bubble diagram was drawn. As shown in Figure 4, the color of the bubble is closely correlated with the P -value: the bluer the bubble, the smaller the P -value, indicating a stronger correlation. The larger the value, the larger the bubble. As a result of GO enrichment, the first 10 counts of each item are ranked in a bar chart (Fig. 5). The counts in the chart are shown on the horizontal axis, and the names of pathways are shown on the vertical axis. The color of the bar chart is closely related to the P -value.

Molecular docking verification

The top 10 key active ingredients in the PPI network were docked with the top seven core targets, and the results are shown in Figure 6. The binding energies of the key active ingredients and core targets were all less than -5.0 kcal/mol ($1 \text{ kcal} = 4.184 \text{ J}$), and the binding energies of most results were less than -7.0 kcal/mol, which indicates that the key active ingredients and core targets have good binding ability, with most showing strong binding affinity, as shown in Table 2. These results suggest that most of the active ingredients in *Lycium barbarum* can spontaneously bind to the core target protein, thereby playing a therapeutic role in liver cancer. The results of the minimum binding energy were visualized, as shown in Figure 7, using PyMOL software for molecular docking. In the figure, the blue represents the small molecular ligand, and the gray represents the amino acid residues of the protein. The two are combined by hydrophobic forces, and the marked number indicates the distance between the carbon atoms of the force.

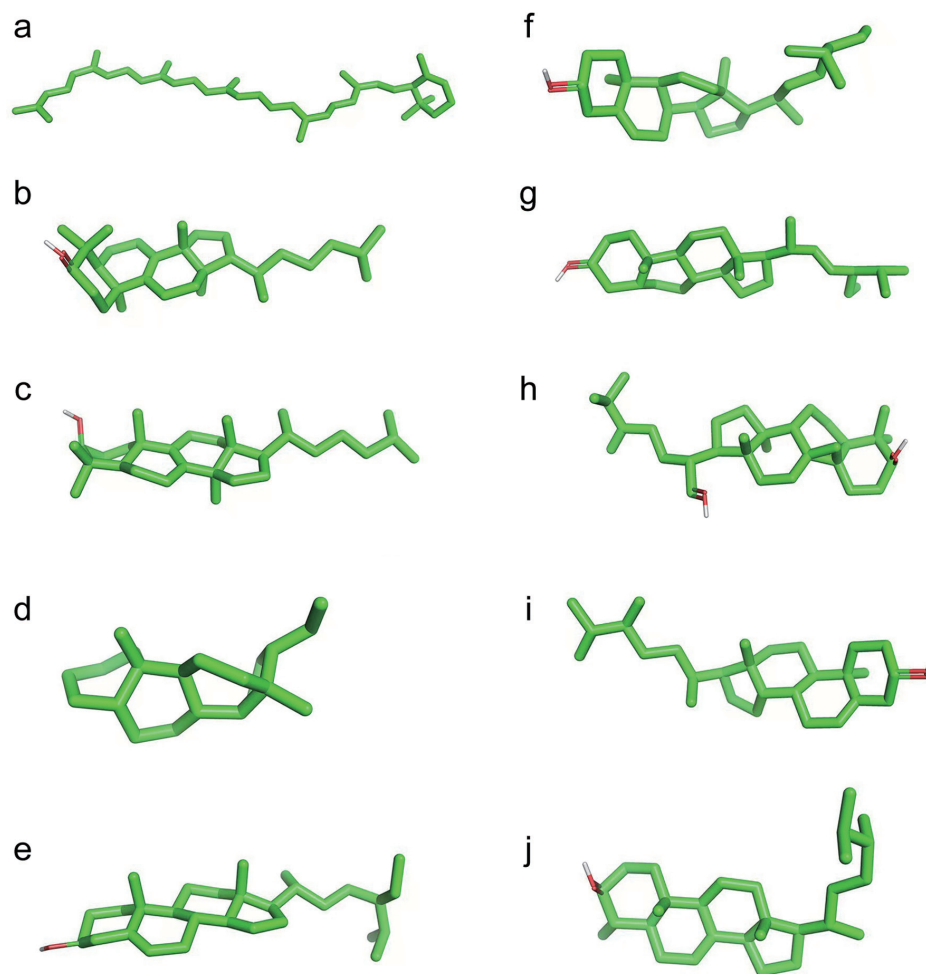


Fig. 1. Top 10 key active ingredient structures. (a) δ -carotene; (b) lano-8-enol; (c) lano-8-ene-3 β -ol; (d) 14b-pregnane; (e) β -sitosterol; (f) carotenin; (g) 24-ethylcholester-22-enol; (h) 24-methylene cycloanthrane-3 β ,21-diol; (i) canolasterol; (j) 24-methylphenol.

Discussion

The role of wolfberry active ingredients in the treatment of liver cancer was predicted based on previous network pharmacology

Lycium chinensis liver cancer

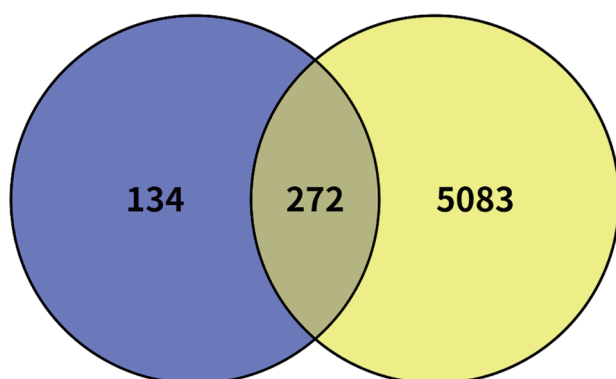


Fig. 2. Venn diagram of Lycium-liver cancer.

studies.⁹ Key active components of Lycium berry were identified, including delta-carotene, lanost-8-enol, lanost-8-en-3 β -ol, 14b-pregnane, and beta-sitosterol, among others. It has been shown that some of these active ingredients have anticancer potential,¹⁰ with β -sitosterol alleviating oxidative stress and chronic liver injury induced by carbon tetrachloride in rats,¹¹ and carotenoids demonstrating protective effects on hepatocytes and the liver.¹²

Core targets include AKT1, TNF, EGFR, ESR1, SRC, PPARG, and HSP90AA1, with AKT1 gene polymorphism potentially being closely related to the occurrence of primary liver cancer.¹³ In the early stages of liver cancer, TNF can promote tumor development by stimulating the proliferation of oval cells (liver stem cells), and TNF may also facilitate tumor metastasis by inducing epithelial-mesenchymal transition.¹⁴ EGFR is highly expressed in many tumors, and its positive expression is correlated with the pathological grade of serum alpha-fetoprotein (AFP)-negative hepatocellular carcinoma, affecting the occurrence, development, and prognosis of serum AFP-negative hepatocellular carcinoma to some extent.¹⁵ Furthermore, cell experiments have confirmed that the proliferation and invasion ability of liver cancer cells significantly increase, and apoptosis is weakened, following ESR1 knockdown, suggesting that ESR1 may be an effective potential target for liver cancer treatment.¹⁶ These intersection targets are

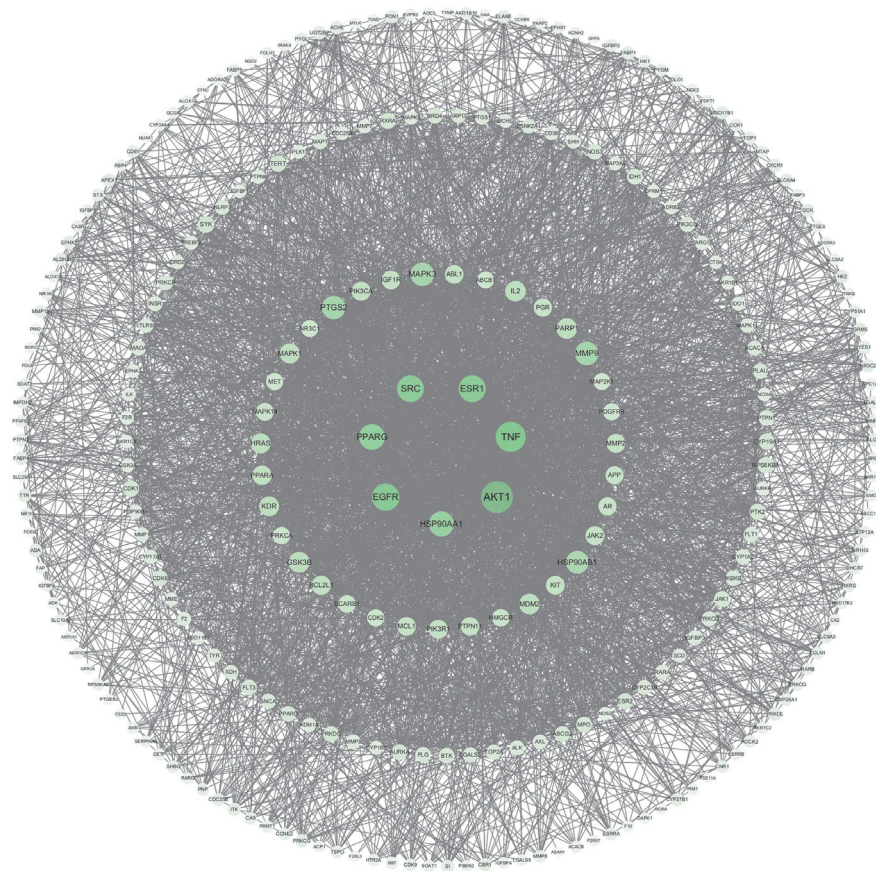


Fig. 3. Optimization of interaction network between the protein of Wolfberry active ingredients and liver cancer.

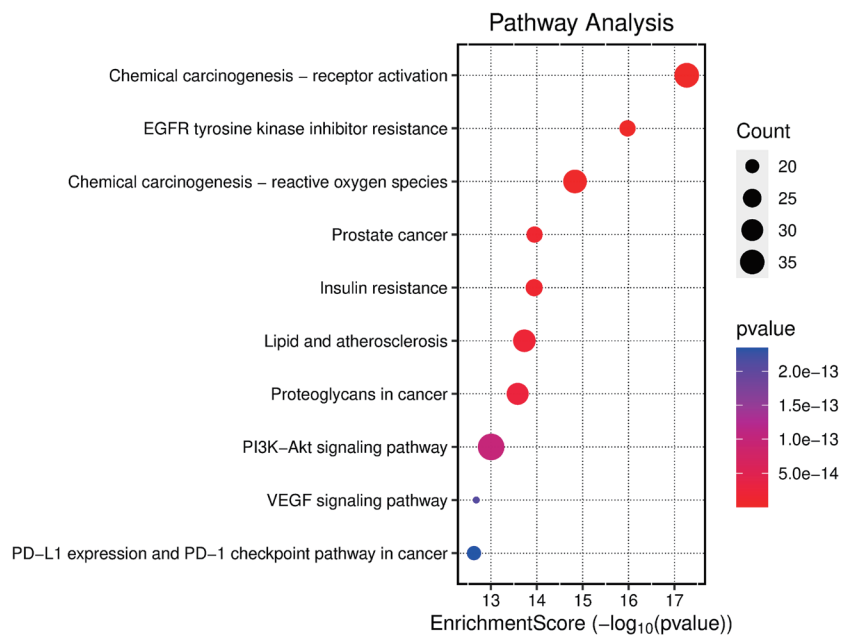


Fig. 4. The top 10 signaling pathways of KEGG enrichment related to *Lycium barbarum* treatment of liver cancer. EGFR, epidermal growth factor receptor; KEGG, Kyoto Encyclopedia of Genes and Genomes; PD-1, programmed death receptor 1; PD-L1, programmed cell death ligand 1; VEGF, vascular endothelial growth factor.

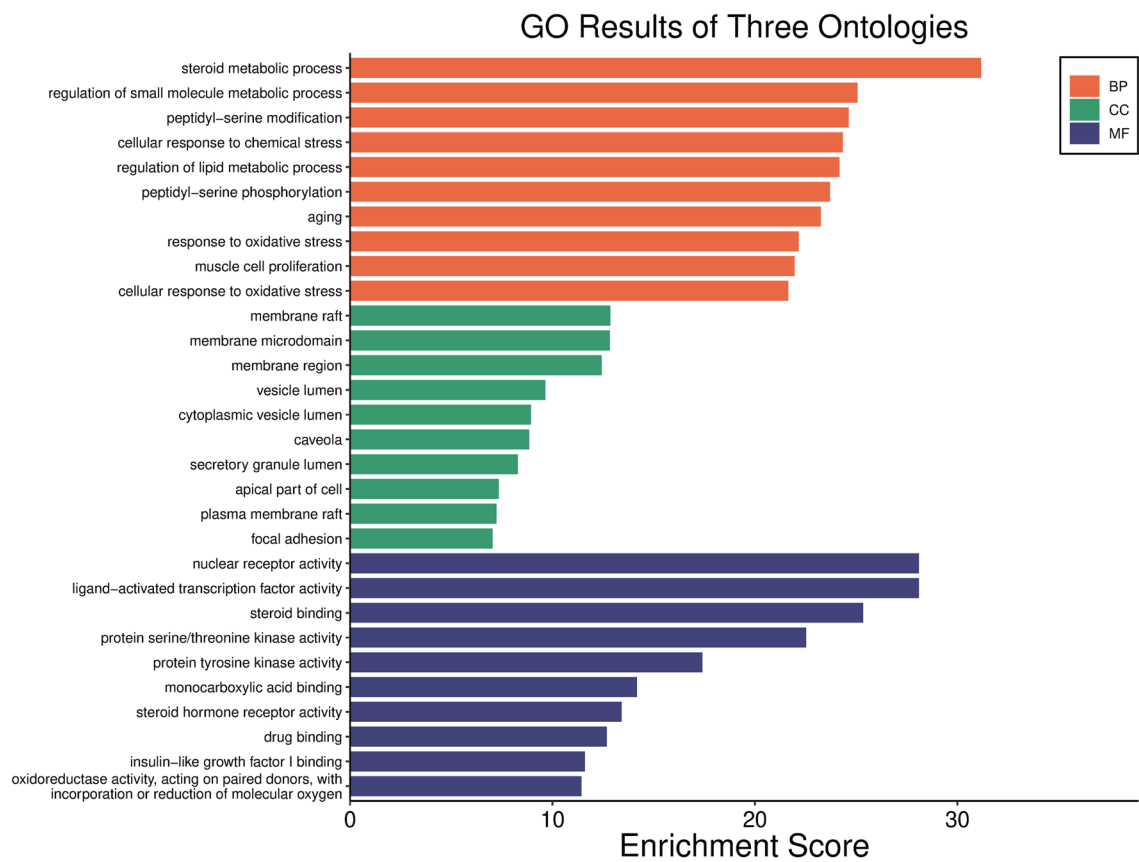


Fig. 5. Top 10 GO-enrichment signaling pathways of *Lycium barbarum* therapy for liver cancer. BP, biological process; CC, cellular components; GO, gene ontology; MF, molecular functions.

likely to be key targets of *Lycium barbarum* in the treatment of liver cancer.

Limitations

Although network pharmacology and molecular docking research

methods reveal the association between drug targets and diseases to a certain extent, they cannot accurately reflect the precise process by which drugs exert drugs in the body. In addition, network pharmacology and molecular docking studies rely on a large number of publicly available bioinformatics databases of various websites for analysis, some of which may have maintenance problems

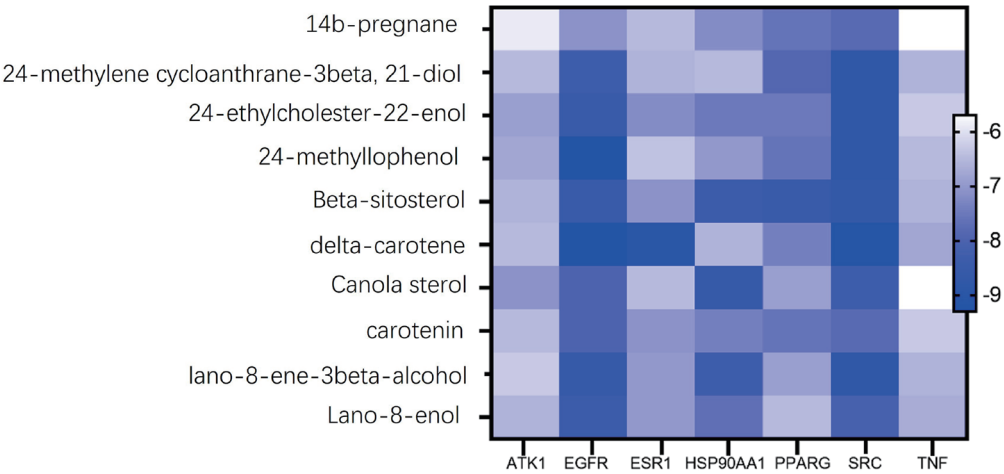


Fig. 6. The docking results of key active ingredients and core target protein molecules. ATK1, serine/threonine kinase 1; EGFR, epidermal growth factor receptor; ESR1, estrogen receptor 1; PPARG, peroxisome proliferator activated receptor gamma.

Key active ingredient	AKT1	EGFR	ESR1	HSP90AA1	PPARG	SRC	TNF
	1uNR	3poz	1xpc	1byq	3u9q	1mfk	4tsv
14b-pregnane	-5.9	-7.1	-6.5	-7.2	-7.6	-7.8	-5.7
24-methylene cycloanthrane-3beta, 21-diol	-6.5	-8.3	-6.6	-6.5	-7.9	-8.8	-6.6
24-ethylcholester-22-enol	-6.9	-8.5	-7.2	-7.5	-7.5	-8.8	-6.3
24-methyllophenol	-6.8	-9.3	-6.4	-7	-7.6	-8.8	-6.5
Beta-sitosterol	-6.6	-8.5	-7.1	-8.4	-8.5	-8.7	-6.6
delta-carotene	-6.5	-9.3	-9	-6.6	-7.4	-9.2	-6.8
Canola sterol	-7.1	-8	-6.5	-8.6	-6.9	-8.3	-5.7
carotenin	-6.5	-8	-7.1	-7.4	-7.6	-7.8	-6.3
lano-8-ene-3beta-alcohol	-6.3	-8.6	-7	-8.3	-6.9	-8.8	-6.6
Lano-8-enol	-6.6	-8.4	-7	-7.7	-6.5	-8.1	-6.7

Acknowledgments

We sincerely appreciate the data support provided by the TCMSP database, PDB database, and other databases during the research process, which facilitated the smooth progress of the study. These extensive data resources have laid a solid foundation for the writing of this paper.

Funding

This study is supported by the project of the Natural Science Foundation of Hebei Province (No: H2022209048).

Conflict of interest

The authors have no conflicts of interest to declare.

Author contributions

Study conception and design (SL, ML), main data analysis, and manuscript draft (ML, JL, KY, QY, SL). All authors contributed to the article and approved the final version.

Ethical statement

Not applicable.

Data sharing statement

After publication, all major data sheets will be available upon request.

References

- [1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, *et al*. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024;74(3):229–263. doi:10.3322/caac.21834, PMID:38572751.
- [2] Lou L, Chen G, Zhong B, Liu F. *Lycium barbarum* polysaccharide induced apoptosis and inhibited proliferation in infantile hemangioma endothelial cells via down-regulation of PI3K/AKT signaling pathway. *Biosci Rep* 2019;39(8):BSR20191182. doi:10.1042/BSR20191182, PMID:31383785.
- [3] Miao Y, Xiao B, Jiang Z, Guo Y, Mao F, Zhao J, *et al*. Growth inhibition and cell-cycle arrest of human gastric cancer cells by *Lycium barbarum* polysaccharide. *Med Oncol* 2010;27(3):785–790. doi:10.1007/s12032-009-9286-9, PMID:19669955.
- [4] Zhu CP, Zhang SH. *Lycium barbarum* polysaccharide inhibits the proliferation of HeLa cells by inducing apoptosis. *J Sci Food Agric* 2013;93(1):149–156. doi:10.1002/jsfa.5743, PMID:22696075.
- [5] Hao Z, Li Z, Huo J, Li J, Liu F, Yin P. Effects of Chinese wolfberry and Astragalus extract on the antioxidant capacity of Tibetan pig liver. *PLoS One* 2021;16(1):e0245749. doi:10.1371/journal.pone.0245749, PMID:33503027.
- [6] Naji S, Zarei L, Pourjabali M, Mohammadi R. The Extract of *Lycium depressum* Stocks Enhances Wound Healing in Streptozotocin-Induced Diabetic Rats. *Int J Low Extrem Wounds* 2017;16(2):85–93. doi:10.1177/1534734617700538, PMID:28682729.
- [7] Wang H, Li Y, Liu J, Di D, Liu Y, Wei J. Hepatoprotective effect of crude polysaccharide isolated from *Lycium barbarum* L. against alcohol-induced oxidative damage involves Nrf2 signaling. *Food Sci Nutr* 2020;8(12):6528–6538. doi:10.1002/fsn3.1942, PMID:33312537.
- [8] Kaur T, Madgulkar A, Bhalekar M, Asgaonkar K. Molecular Docking in Formulation and Development. *Curr Drug Discov Technol* 2019;16(1):30–39. doi:10.2174/1570163815666180219112421, PMID:29468973.
- [9] Liu M, Zhang Y, Yu K, Li S, Li J. The Mechanism of *Lycium Barbarum* for Liver Cancer Treatment Was Analyzed Based on Network Pharmacology. *Clinical Medicine Frontiers* 2024;3(3):52–60. doi:10.57237/j.cmf.2024.03.001.
- [10] Zhu PF, Dai Z, Wang B, Wei X, Yu HF, Yan ZR, *et al*. The Anticancer Activities Phenolic Amides from the Stem of *Lycium barbarum*. *Nat Prod Bioprospect* 2017;7(6):421–431. doi:10.1007/s13659-017-0134-x, PMID:28589416.
- [11] Zheng L, He C, Jiang Y, Ren T, Liang S, He H. Mechanism of *Scutellaria baicalensis* regulating ferroptosis to reverse tumor drug resistance based on network pharmacology and experimental verification. *Drugs & Clinic* 2023;38(3):519–530. doi:10.7501/j.issn.1674-5515.2023.03.005.
- [12] Ji M, Wei W, Zhang K, Jin J, Guo T. Research progress on carotenoids in *Lycium barbarum*. *West China J Pharm Sci* 2024;39(1):99–102. doi:10.13375/j.cnki.wcjs.2024.01.021.
- [13] Tian L, Xie H, Sun G. Case-control study of primary hepatic carcinoma and rs1130214 of AKT1 gene polymorphism. *Journal of Xinjiang Medical University* 2016;39(6):757–759. doi:10.3969/j.issn.1009-5551.2016.06.023.
- [14] Jang DI, Lee AH, Shin HY, Song HR, Park JH, Kang TB, *et al*. The Role of Tumor Necrosis Factor Alpha (TNF- α) in Autoimmune Disease and Current TNF- α Inhibitors in Therapeutics. *Int J Mol Sci* 2021;22(5):2719. doi:10.3390/ijms22052719, PMID:33800290.
- [15] Xu T, Ding Y, Gao S, Fang X, Li Y, Liao L. Expression of EGFR in serum AFP negative hepatocellular carcinoma and its relationship with clinicopathological and prognosis. *Journal of Hepatobiliary Surgery* 2022;28(5):356–359.
- [16] Meng J, Wang L, Hou J, Yang X, Lin K, Nan H, *et al*. CCL23 suppresses liver cancer progression through the CCR1/AKT/ESR1 feedback loop. *Cancer Sci* 2021;112(8):3099–3110. doi:10.1111/cas.14995, PMID:34050704.