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Pterostilbene Inhibits Hepatocellular Carcinoma by Regulating the MAPK Signaling Pathway

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Abstract: To explore the mechanism by which pterostilbene inhibits hepatocellular carcinoma (HCC), this study adopted the method of network pharmacology. The intersection targets of pterostilbene and HCC were obtained through database screening, the protein-protein interaction (PPI) network was constructed to screen core targets, and then GO functional enrichment analysis and KEGG pathway enrichment analysis were carried out. The results showed that a total of 88 intersection targets and 10 core targets including MAPK1 were identified. These targets were mainly enriched in biological processes such as protein phosphorylation and MAPK cascade reaction, and the core regulatory pathway was the MAPK signaling pathway. This study indicates that pterostilbene may exert anti-HCC effects by targeting and regulating the MAPK signaling pathway through the synergistic action of multiple targets and multiple pathways, which provides a theoretical reference for its subsequent research and application.

1. Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide, accounting for 90% of primary liver cancers [1]. Its incidence is on the rise, with strong heterogeneity and high recurrence rate. The efficacy of surgery and immunotherapy is limited, and the response rate of immunotherapy is only 15%-30% [2]. Risk factors include hepatitis virus infection, aflatoxin contamination, and metabolic-associated fatty liver disease (MAFLD). Lactylation modification and abnormal cholesterol metabolism are the key mechanisms for its progression [3]. As a natural active component, pterostilbene can exert anti-HCC effects by regulating related signaling pathways, improving the tumor immune microenvironment, and intervening in metabolic abnormalities, which provides new ideas for the treatment of HCC.

Pterostilbene (PTS) is a natural stilbene compound derived from berries such as blueberries and blackberries, and a variety of Chinese herbal medicines. It is a methylated derivative of resveratrol, with multiple effects such as improving cell metabolism [4], enhancing antioxidant function [5], and alleviating tissue damage [6]. Previous studies have shown that in a high-fat model, pterostilbene can reduce hepatitis in mice by up-regulating GSH activity and reducing MDA production, which may be related to activating the Nrf2 signaling pathway, improving oxidative stress and endoplasmic reticulum stress [7]. Meanwhile, pterostilbene can reduce the increase of serum ALT, TBil and BUN

levels in mice induced by ZEA, alleviate inflammatory infiltration and other damages in liver and kidney tissues, and also improve intestinal damage by regulating intestinal flora and enhancing the intestinal epithelial mucosal barrier [8]. This study predicted and analyzed the mechanism of pterostilbene in alleviating HCC by means of network pharmacology, which provides ideas and directions for further research.

2. Materials and Methods

2.1 Selection of Pterostilbene and HCC-related Targets

With "Hepatocellular Carcinoma" as the keyword, human HCC-related gene targets were obtained from the GeneCards database (https://www.genecards.org/) [9], and the final disease target set was obtained through median screening. The SMILES number of pterostilbene was obtained from the Pubchem database (https://pubchem.ncbi.nlm.nih.gov/) [10] with "Pterostilbene" as the keyword, which was imported into SwissTargetPredict (http://swisstargetprediction.ch/) [11] for prediction to obtain its related action targets. A total of 88 intersection targets of pterostilbene and HCC were finally identified.

2.2 Construction of Protein-Protein Interaction (PPI) Network

Venn analysis tool (https://www.bic.ac.cn/test/venn/#/) was used to perform intersection analysis on pterostilbene and HCC targets, draw a Venn diagram and determine therapeutic targets. The 88 intersection targets were imported into the STRING 11.0 database (https://string-db.org) [12], with the biological species set as "Homo sapiens", confidence > 0.7, unconnected nodes hidden, and other parameters default to construct the PPI network. Cytoscape 3.10.0 [13] software was used to realize the visualization of the PPI network. The core target interaction relationship showed that PIK3CA, PRKACA, MAPK1, ESR1, RAF1, EGFR, BCL2, MAPK8, RELA and MAPK14 were key interaction nodes.

2.3 Functional and Pathway Enrichment Analysis of Pterostilbene and HCC Targets

Metascape platform (https://metascape.org/gp/index.html) was used for functional and pathway enrichment analysis of intersection targets. The microbioinformatics platform (https://www.bioinformatics.com.cn) was used to generate the GO functional analysis histogram and KEGG pathway enrichment analysis bubble chart. GO analysis included three dimensions: biological process (BP), cellular component (CC) and molecular function (MF).

3. Results

3.1 Selection of Pterostilbene and HCC-related Targets

Potential molecular targets of pterostilbene in improving HCC were screened by network pharmacology analysis. Pterostilbene-related genes were determined by SwissTargetPrediction and other databases, and HCC-related genes were obtained from GeneCards and other databases. 88 common targets were identified by intersection analysis and a Venn diagram was drawn (Figure 1). The PPI network was constructed (Figure 2), and the core interaction nodes were identified as PIK3CA, PRKACA, MAPK1, ESR1, RAF1, EGFR, BCL2, MAPK8, RELA and MAPK14, including 10 key core targets.

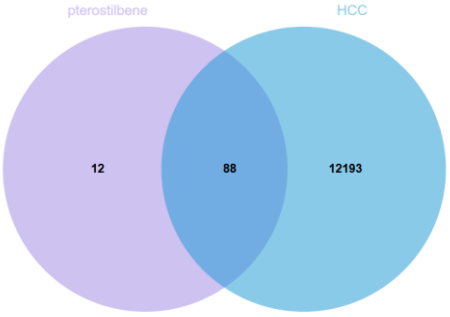

Figure 1 Venn diagram of target intersection between pterostilbene and HCC

3.2 PPI Network and Core Target Identification

Based on the 88 intersection targets, a PPI network was constructed (Figure 2). The Top10 core interaction targets were obtained by sorting with the MCC algorithm, which were BCL2 (984), MAPK1 (868), ESR1 (708), RELA (666), PRKACA (666), PRKACB (610), MAPK8 (580), MAPK14 (432), RAF1 (372) and BRAF (372) in descending order of scores (Figure 3). Among them, BCL2 had the largest number of connected proteins, and MAPK1, ESR1, RELA and others were closely associated with a large number of additional proteins, forming a protein-protein interaction (PPI) network composed of multiple nodes and multiple edges.

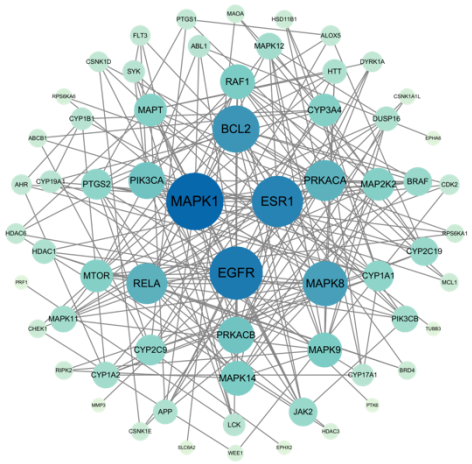

Figure 2 Visualization diagram of PPI network of intersection targets between pterostilbene and HCC

Rank	Name	Score
1	BCL2	984
2	MAPK1	868
3	ESR1	720
4	RELA	708
5	PRKACA	666
6	PRKACB	610
7	MAPK8	580
8	MAPK14	438
9	RAF1	432
10	BRAF	372

Figure 3 Score diagram of Top10 core targets of intersection targets between pterostilbene and HCC by MCC algorithm

3.3 Functional and Pathway Enrichment Analysis of Pterostilbene and HCC Targets

The results of GO enrichment analysis (Figure 4) showed that the potential targets of pterostilbene in intervening in HCC presented obvious aggregation characteristics at the functional level. In biological processes (BP), the targets were mainly enriched in protein phosphorylation, phosphorylation regulation, MAPK cascade reaction, enzyme-linked receptor signaling pathway, cellular response to nitrogen compounds and protein modification processes, with signal transduction and post-translational modification regulation of proteins as the core. Cellular component (CC) showed that these targets were mostly located in structures such as the perinuclear region of cytoplasm, membrane raft, membrane microdomain, receptor complex and serine/threonine protein kinase complex, which were highly related to the initiation of signal molecules, transmembrane transduction and energy metabolism sites. Molecular function (MF) suggested that the targets mainly had protein kinase activity, serine/threonine kinase activity, phosphotransferase activity, MAP kinase activity, and also involved in heme binding, steroid hydroxylation and flavin-dependent monooxygenase and other functions, focusing on kinase catalytic activity and oxidation metabolism-related functions.

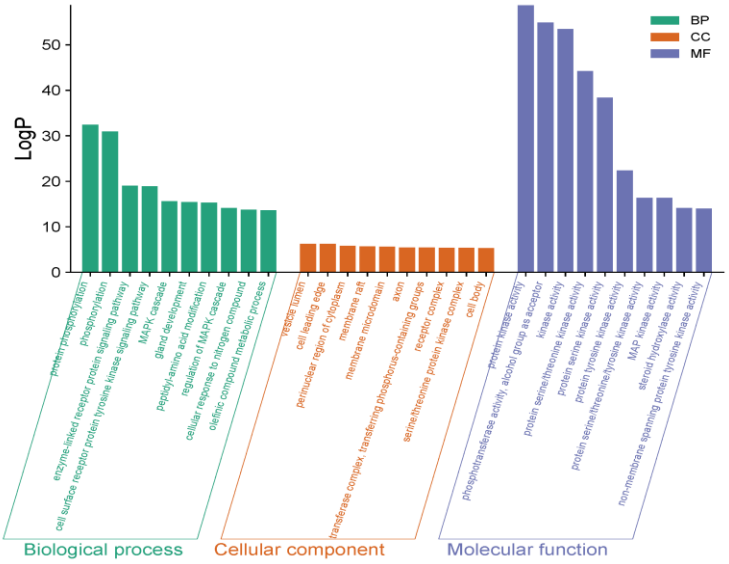

Figure 4 Histogram of GO functional enrichment analysis of intersection targets between pterostilbene and HCC

The results of KEGG pathway enrichment analysis (Figure 5) further identified a variety of signal pathways highly related to the disease. The key pathways with statistical significance included the MAPK signaling pathway, pathways in cancer, PD-L1 expression and PD-1 checkpoint pathway, and TNF signaling pathway. The MAPK signaling pathway was identified as the core effector pathway. Based on the above results, a schematic diagram of the molecular mechanism of pterostilbene exerting anti-HCC effects by targeting this pathway was constructed to intuitively show its potential regulatory mode.

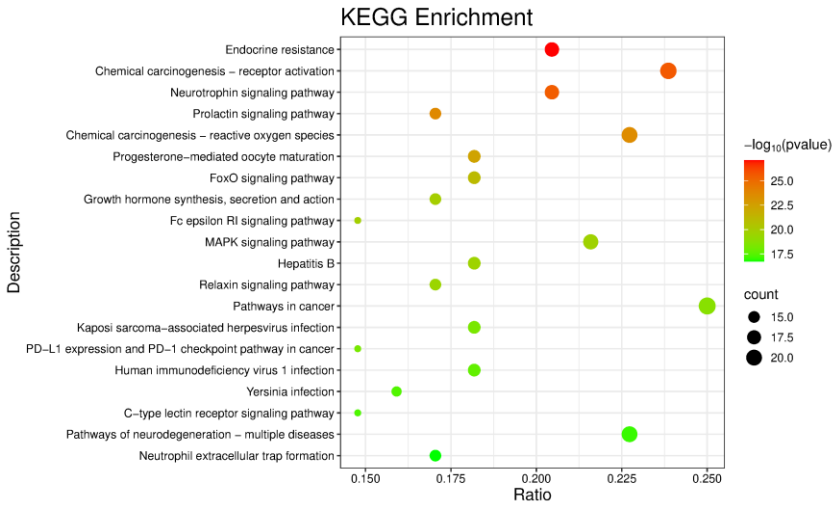

Figure 5 Bubble chart of KEGG pathway enrichment analysis of intersection targets between pterostilbene and HCC

4. Conclusions

As a natural stilbene compound, pterostilbene has a similar structure to resveratrol and possesses a variety of pharmacological activities such as anti-inflammatory, antioxidant and anti-tumor effects. It can inhibit a variety of tumors by regulating cell proliferation, apoptosis, inflammation and immune response, and its anti-HCC potential has attracted much attention[14].

This study initially clarified the 88 intersection targets and core action forms of pterostilbene in improving HCC by network pharmacology, and confirmed that it can intervene in the HCC process through the synergistic effect of multiple targets and multiple pathways. The core interaction targets include 10 genes such as BCL2, MAPK1, ESR1 and RELA, and targets such as EGFR, PIK3CA, PTGS2 and JAK2 are involved in regulation together. These targets are mainly enriched in biological processes such as protein phosphorylation and MAPK cascade reaction, with serine/threonine kinase activity and flavin-dependent monooxygenase activity as the core molecular functions, and concentrated in key pathways such as the MAPK signaling pathway, pathways in cancer, PD-L1 expression and PD-1 checkpoint pathway, and TNF signaling pathway. The above results indicate that pterostilbene is highly related to anti-cancer activity, and it may exert anti-HCC effects by participating in oxidative stress and reactive oxygen species synthesis, and regulating protein kinase phosphorylation.

Among them, the MAPK signaling pathway, as the core effector pathway of pterostilbene against HCC identified in this study, is a key signal network regulating cell proliferation, differentiation, apoptosis and stress response in eukaryotic cells[15], mainly including three subfamilies: ERK, JNK and p38-MAPK, corresponding to MAPK1 (ERK2), MAPK8 (JNK1) and MAPK14 (p38α) in the core targets of this study respectively. Their abnormal activation plays a key driving role in the whole process of HCC occurrence, development, invasion and metastasis[16]. In the pathological process of HCC, inducing factors such as hepatitis virus infection, oxidative stress and metabolic abnormalities can activate the RAF-MEK-ERK pathway through upstream receptors[17]. Over-activated MAPK1 can promote the malignant proliferation, epithelial-mesenchymal transition and angiogenesis of tumor cells, and enhance the invasive and metastatic ability of liver cancer cells[18]; the abnormal activation of the JNK/p38-MAPK pathway can regulate the release of inflammatory factors, promote the remodeling of the tumor microenvironment, and mediate the activation of the anti-apoptotic signal pathway, making liver cancer cells escape apoptosis monitoring, and also participate in the

formation of drug resistance of liver cancer cells to chemotherapy and immunotherapy[19]. Pterostilbene can target MAPK1, MAPK8, MAPK14 and the upstream regulatory target RAF1, suggesting that it may directly inhibit the activity of each core kinase of the MAPK signaling pathway, block the abnormal phosphorylation cascade reaction of the pathway, inhibit the pro-tumor function of the pathway from multiple nodes upstream to downstream[20], and then realize the inhibition of liver cancer cell proliferation and the induction of apoptosis.

In addition, the MAPK signaling pathway has a close cross-regulatory relationship with the TNF signaling pathway and PD-L1 expression and PD-1 checkpoint pathway. The activation of the MAPK pathway can further promote the release of inflammatory cytokines in the tumor microenvironment through the nuclear transcription factor RELA (NF-κB p65), maintain the chronic inflammatory state mediated by the TNF signaling pathway[21], and simultaneously up-regulate the expression of PD-L1 on the surface of liver cancer cells to achieve tumor immune escape[22]. Pterostilbene can indirectly inhibit the pro-tumor effects of downstream related pathways by targeting and regulating the MAPK signaling pathway, forming a multi-pathway synergistic regulatory anti-HCC mode. The TNF signaling pathway is closely related to the maintenance of the tumor inflammatory microenvironment, and the PD-L1 expression and PD-1 checkpoint pathway are involved in tumor immune escape, suggesting that pterostilbene may exert anti-HCC effects by targeting and inhibiting these pro-tumor signal pathways, blocking the malignant proliferation and metastasis of tumor cells, reducing the local inflammatory response of the liver and reversing immune escape[23].

In summary, pterostilbene may act on 88 intersection targets such as BCL2, MAPK1, EGFR and PIK3CA, with kinase-mediated phosphorylation signal regulation as the core, focus on targeting and inhibiting the abnormal activation of the MAPK signaling pathway, and simultaneously combine with oxidative metabolism and hormone metabolism regulation, synergistically regulate key pathways such as the cancer pathway, TNF signaling pathway, PD-L1 expression and PD-1 checkpoint pathway, exert anti-tumor effects such as inhibiting cell proliferation, inducing cell apoptosis, reducing inflammatory response and reversing immune escape, reflecting the characteristics of multi-target and multi-pathway combined intervention. However, this study has limitations. Network pharmacology analysis has inherent deficiencies, and the absorption, distribution, metabolism and excretion processes of pterostilbene in vivo are not considered. Follow-up studies need to further verify the regulatory effect of pterostilbene on the expression and phosphorylation level of each kinase in the MAPK signaling pathway through cellular and animal experiments, and clarify the dose-effect relationship and specific action mechanism of its anti-HCC effect.

References

[1] Sung, H., et al., Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin, 2021. 71(3): p. 209-249.

[2] Pham, T., et al., STAT3 and p53: Dual Target for Cancer Therapy. Biomedicines, 2020. 8(12).

[3] Li, Y., S. Li and C. Lin, Effect of resveratrol and pterostilbene on aging and longevity. Biofactors, 2018. 44(1): p. 69-82.

[4] Boycott, C., et al., AMPK-Dependent Epigenetic Regulation of Metabolism Mediates the Anti-Cancer Action of Pterostilbene in Hepatocellular Carcinoma. Mol Nutr Food Res, 2025. 69(23): p. e70217.

[5] Hseu, Y., et al., The in vitro and in vivo depigmenting activity of pterostilbene through induction of autophagy in melanocytes and inhibition of UVA-irradiated alpha-MSH in keratinocytes via Nrf2-mediated antioxidant pathways. Redox Biol, 2021. 44: p. 102007.

[6] Shen, B., et al., Pterostilbene alleviated NAFLD via AMPK/mTOR signaling pathways and autophagy by promoting Nrf2. Phytomedicine, 2023. 109: p. 154561.

[7] Fan, X., et al., Pterostilbene Reduces Acetaminophen-Induced Liver Injury by Activating the Nrf2 Antioxidative Defense System via the AMPK/Akt/GSK3beta Pathway. Cell Physiol Biochem, 2018. 49(5): p. 1943-1958.

[8] Guo, C., A. Kumar and C. Liao, Pterostilbene Exhibited the Anticancer Effect Against 1, 2-Dimethylhydrazine

(DMH)-Induced Colorectal Cancer via Alteration of Oxidative Stress, Inflammation and Gut Microbiota. J Biochem Mol Toxicol, 2025. 39(3): p. e70123.
[9] Stelzer, G., et al., The GeneCards Suite: From Gene Data Mining to Disease Genome Sequence Analyses. Curr Protoc Bioinformatics, 2016. 54: p. 1.30.1-1.30.33.
[10] Kim, S., et al., PubChem in 2021: new data content and improved web interfaces. Nucleic Acids Res, 2021. 49(D1): p. D1388-D1395.
[11] Daina, A., O. Michielin and V. Zoete, SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules. Nucleic Acids Res, 2019. 47(W1): p. W357-W364.
[12] Szklarczyk, D., et al., The STRING database in 2021: customizable protein-protein networks, and functional characterization of user-uploaded gene/measurement sets. Nucleic Acids Res, 2021. 49(D1): p. D605-D612.
[13] Shannon, P., et al., Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res, 2003. 13(11): p. 2498-2504.
[14] Qu, X., L. Zhang and L. Wang, Pterostilbene as a Therapeutic Alternative for Central Nervous System Disorders: A Review of the Current Status and Perspectives. J Agric Food Chem, 2023. 71(40): p. 14432-14457.
[15] Zhang, M. and S. Zhang, Mitogen-activated protein kinase cascades in plant signaling. J Integr Plant Biol, 2022. 64(2): p. 301-341.
[16] Fang, J.Y. and B.C. Richardson, The MAPK signalling pathways and colorectal cancer. Lancet Oncol, 2005. 6(5): p. 322-327.
[17] Ullah, R., et al., RAF-MEK-ERK pathway in cancer evolution and treatment. Semin Cancer Biol, 2022. 85: p. 123-154.
[18] Deng, R., et al., MAPK1/3 kinase-dependent ULK1 degradation attenuates mitophagy and promotes breast cancer bone metastasis. Autophagy, 2021. 17(10): p. 3011-3029.
[19] Wu, Y., et al., A network pharmacology approach and experimental validation to investigate the anticancer mechanism of Qi-Qin-Hu-Chang formula against colitis-associated colorectal cancer through induction of apoptosis via JNK/p38 MAPK signaling pathway. J Ethnopharmacol, 2024. 319(Pt 3): p. 117323.
[20] Meng, X. and S. Zhang, MAPK cascades in plant disease resistance signaling. Annu Rev Phytopathol, 2013. 51: p. 245-266.
[21] Zhang, T., et al., NF-kappaB signaling in inflammation and cancer. MedComm (2020), 2021. 2(4): p. 618-653.
[22] Tobias, J., et al., Emerging targets for anticancer vaccination: PD-1. ESMO Open, 2021. 6(5): p. 100278.
[23] Ai, L., et al., Research Status and Outlook of PD-1/PD-L1 Inhibitors for Cancer Therapy. Drug Des Devel Ther, 2020. 14: p. 3625-3649.