Genesis Journal of Surgery and Medicine

Genesis-GJSM-2(2)-18
Volume 2 | Issue 2
Open Access
ISSN: 3049-2254

The Role of Statins in Inhibiting Hepatocellular Carcinoma

Shi-Ze Xiong[1,2,3], Dong-Ge Han[1,2,3] and Wei Liu[1,2,3*]

[1]The First College of Clinical Medical Science, China Three Gorges University, Yichang, China
[2]Institute of Digestive Disease, China Three Gorges University, Yichang, China
[3]Department of Gastroenterology, Yichang Central People's Hospital, Yichang, China

[*]**Corresponding author:** Wei Liu, Ph.D., Institute of Digestive Disease, China Three Gorges University, 8 Daxue Road, Yichang 443000, China.

Citation: Xiong SZ, Han DG, Lie W, (2023) The Role of Statins in Inhibiting Hepatocellular Carcinoma. Genesis J Surg Med. 2(2):1-10.

Received: October 6, 2023 | **Published:** November 13, 2023

Abstract

Hepatocellular carcinoma is a common gastrointestinal tumor in clinic, whose five-year survival rate is very low due to its concealed onset and rapid progress. As the rate limiting enzyme HMG CoA reductase inhibitor, statins are the most common lipid-lowering drugs in clinic to prevent cardiovascular diseases. More and more basic and clinical studies have shown that statins have preventive and therapeutic effects on a variety of tumors. Here, we summarize the research progress of statins in the prevention and treatment of hepatocellular carcinoma.

Keywords

Statins; Hepatocellular carcinoma; Research progress

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, but has the second highest mortality rate. China has a high incidence of hepatocellular carcinoma, with approximately half of the global cases of hepatocellular carcinoma being diagnosed in China. The main treatment options for hepatocellular carcinoma include liver transplantation, surgical resection and local ablation. Most patients miss the opportunity for surgery at the time of diagnosis. Local ablation therapy has a five-year recurrence rate of up to 70%, and some patients terminate liver transplantation due to tumor progression. That is why it is crucial to investigate methods of preventing and treating hepatocellular carcinoma.

In the 1970s, Japanese researchers discovered 3-hydroxy-3methylglutaryl coenzyme A reductase inhibitors in fungal culture, which inhibit cholesterol synthesis. Since then, varieties of statins have been developed and have made a major contribution to the prevention of cardiovascular diseases. In recent years, it has been found that statins can inhibit the development of hepatocellular carcinoma, in addition to lowering blood lipids [1]. The following section summarizes the research progress of statins in the prevention and treatment of hepatocellular carcinoma.

Preventive Effect on Hepatocellular Carcinoma by Statins

Hepatocarcinogenesis is mainly associated with viral hepatitis, aflatoxin exposure, alcoholic fatty liver disease, non-alcoholic fatty liver disease and genetic factors. Non-alcoholic fatty liver disease (NAFLD) involves a range of conditions, ranging from simple steatosis to cirrhosis and ultimately, hepatocellular carcinoma. Park et al. fed mice with a diet lacking methionine and choline and found that a variety of statins can prevent hepatic steatosis and non-alcoholic steatohepatitis. The specific mechanism is that statins can promote PPAR α on the oxidative capacity of mitochondrial and peroxidase fatty acids and the preventive effect of statin is independent of its cholesterol-lowering capacity [2]. Tao Zheng et al. used diethylnitrosamine to induce the establishment of a hepatocellular carcinoma model in rats and found that atorvastatin exerts different degrees of anti-tumor effects in the hepatitis-cirrhosis-hepatocellular carcinoma trilogy and inhibits the development of tumourigenesis mainly through the regulation of the tumour microenvironment [3], which is specifically manifested in the following ways: Atorvastatin inhibits hepatic stellate cell activation and proliferation, downregulates TGF-β levels, promotes tumor cell apoptosis, and downregulates VEGFa to inhibit angiogenesis.

Inhibition of Hepatocellular Carcinoma by Statins Alone

Hepatocarcinogenesis is mainly associated with viral hepatitis, aflatoxin exposure, alcoholic fatty liver disease, non-alcoholic fatty liver disease and genetic factors. Non-alcoholic fatty liver disease (NAFLD) involves a range of conditions, ranging from simple steatosis to cirrhosis and ultimately, hepatocellular carcinoma. Park et al. fed mice with a diet lacking methionine and choline and found that a variety of statins can prevent hepatic steatosis and non-alcoholic steatohepatitis. The specific mechanism is that statins can promote PPAR α on the oxidative capacity of mitochondrial and peroxidase fatty acids and the preventive effect of statin is independent of its cholesterol-lowering capacity [2]. Tao Zheng et al. used diethylnitrosamine to induce the establishment of a hepatocellular carcinoma model in rats and found

that atorvastatin exerts different degrees of anti-tumor effects in the hepatitis-cirrhosis-hepatocellular carcinoma trilogy and inhibits the development of tumourigenesis mainly through the regulation of the tumour microenvironment [3], which is specifically manifested in the following ways: Atorvastatin inhibits hepatic stellate cell activation and proliferation, downregulates TGF-β levels, promotes tumor cell apoptosis, and downregulates VEGFa to inhibit angiogenesis.

Inhibition of Hepatocellular Carcinoma by Statins Alone

Effects on the Regulation of Proliferation Signaling Pathways in Hepatocellular Carcinoma Cells

TGF-β1 is a multifunctional cytokine primarily produced by hepatocytes. TGF-β1 is widely involved in various pathophysiological processes and has biological activities, including the regulation of cell proliferation, differentiation, migration, and apoptosis. Ridruejo E et al. discovered that both atorvastatin and simvastatin reversed the pro-proliferative effects of HCB on HepG2 hepatocellular carcinoma cell lines by the mechanism of statin inhibition of the TGF-β1/c-Src pathway and involvement in the regulation of thyroid hormone dynamic homeostasis [4]. As cell cycle protein-dependent kinase inhibitors, p21 and p27 participate in cell proliferation and apoptosis by regulating the cell cycle. Sin-Ting Wang et al. constructed HepG2, Hep3B, and HepG2 hepatocellular carcinoma cell line xenografts in nude mice tumor models, and found that the growth of tumor cells in the simvastatin-treated group was restricted, and the specific mechanism was that statin promotes the expression of p21 by activating AMPK and inhibited the degradation of p27 by negatively modulating the STAT3-Skp2 axis, which ultimately induced the blockage of G0/G1 phase of the hepatocellular carcinoma cell cycle [5].

The Wnt/β-catenin signaling pathway can be involved in various physiopathological processes in the liver, with specific effects depending on downstream target molecules [6]. Xia et al. used different concentrations of simvastatin to act on SMCC-7721 hepatocellular carcinoma cell line, and found that statin significantly inhibited the proliferation of tumor cells in a dose-dependent manner, and the specific mechanism may be that statin down-regulates the expression of c-myc and cyclinD1 through regulating the RIP140/Wnt/β-catenin/TCF4 axis, and ultimately inhibits the liver cancer cell cycle [7]. When Wang et al. used atorvastatin to act on a mouse xenograft model of hepatocellular carcinoma cell lines, they observed that the statin induced G0/G1 phase cell cycle block to promote tumour cell growth inhibition and induced senescence of hepatocellular carcinoma cells, and the mechanism may be related to the down-regulation of hTERT expression by the statin through the inhibition of the IL-6/STAT3 signalling pathway [8].

Modulation of Invasive Metastasis in Hepatocellular Carcinoma Cells

Tumor metastasis is the leading cause of cancer-related deaths, and epithelial-mesenchymal transition (EMT) plays an important role. Integrins are cell surface receptors which mediate cell-to-cell and cell-extracellular matrix interactions. They play a crucial role in tumor cell metastasis and target organ capillary endothelial cell adhesion. Rho-dependent kinase (ROCK) is a Rho GTPase target protein, involved in tumor cell metastasis and invasion. When Borna et al. used simvastatin to act on hepatocellular carcinoma cell lines, they found that statin inhibited tumor cell proliferation and decreased the adhesion rate of tumor cells to human umbilical vein endothelial cells, thus inhibiting tumor invasion and metastasis, and the

mechanism may be related to statin's down-regulation of integrins and ROCK expression [9]. Matrix metalloproteinases (MMPs) comprise a group of zinc-dependent endoproteinases that facilitate the EMT process in malignant tumors. Danie et al. used diethylnitrosamine to induce the establishment of rat hepatocellular carcinoma model, and found that pravastatin can significantly reduce the volume of rat liver tumors, reduce the incidence of lung metastasis and the scope of metastasis, and the mechanism may be related to the reduction of MMP-2 and MMP-9 expression by statin [10]. Osman et al. found that fluvastatin dose-dependently inhibited TGF-β1-induced invasion and metastasis in Hep3B hepatocellular carcinoma cell lines [11].

Regulation of Programmed Cell Death in Hepatocellular Carcinoma Cells

Apoptosis is the most common programmed cell death, which relies on caspase family activation to induce extensive cleavage of hundreds of substrates and rapid cell death. Depending on the different activation pathway, apoptosis can be categorized into endogenous apoptosis and exogenous apoptosis, in which the Bcl-2 protein family is crucial in endogenous apoptosis. Huang et al. demonstrated a marked rise in tumor cell death through simvastatin treatment in HepG2 and Huh7 hepatocellular carcinoma cell lines. This mechanism may be linked to statin-induced up-regulation of Notch1 expression, leading to the promotion of transcription of p53 and Bax and down-regulation of Bcl-2 expression [12]. Zhang et al. used fluvastatin to act on HepG2, SMMC-7721 and MHCC-97H hepatocellular carcinoma cell lines, and found that tumor cell apoptosis was increased in the statin-treated group, with a blockage of the cellular G2/M cycle, and a decrease in invasive metastasis. The mechanism of behind these effects may be related to the activation of the cytochrome c/Caspase-9/Caspase-3 pathway by statin leading to mitochondria-dependent tumor cell apoptosis [13]. You et al. also found that pitavastatin promoted Caspase-9 and Caspase-3 activation to induce apoptosis in hepatocellular carcinoma cells [14].

Inhibition of Hepatocellular Carcinoma by Statins in Combination with Other Treatments

There are numerous treatment options for liver cancer, including surgical resection, liver transplantation, local ablation, radiotherapy and targeted therapy. However, each treatment has its limitations. As liver cancer is susceptible to recurrence and metastasis, patients frequently require a combination of treatments to prolong survival, and a sensible combination of treatments and effective adjuvant therapies are particularly important.

Combined with Surgical Treatment

Surgical resection represents the most effective radical therapy for patients with early-stage hepatocellular carcinoma. Nevertheless, the high recurrence rate after surgery poses a persistent challenge. Takahiro et al. retrospectively analyzed 643 patients with hepatocellular carcinoma who underwent initial radical hepatectomy at Kyoto University Hospital from January 2000 to December 2014 and found that perioperative application of statins prolonged recurrence-free survival after radical hepatectomy [15]. Liver transplantation has the advantage of low recurrence rate and high quality of survival compared to other treatments, however, once recurrence occurs the 5-year survival rate is extremely low. Cho et al. performed a time-dependent Cox regression analysis of 347 patients who underwent liver transplantation for hepatocellular carcinoma and found that receipt of statin therapy was

associated with a significantly lower risk of recurrence of hepatocellular carcinoma after correction for other risk factors (hazard ratio = 0.32, 95% CI = 0.11-0.89) [16].

Combined with Chemotherapy

Chemotherapy is one of the most important treatments for advanced hepatocellular carcinoma. As a downstream effector of the hippopotamus signaling pathway, high expression of YAP1 is believed to be associated with hepatocellular carcinoma progression and chemotherapy resistance. GUO et al. used atorvastatin in combination with cisplatin to treat HepG2 and Huh-7 hepatocellular carcinoma cell lines and found that statin significantly increased the sensitivity of tumor cells to cisplatin. The specific mechanism may be that statin induces tumor cell apoptosis by downregulating YAP1 to activate Caspase-9 and Caspase-3[17]. For unresectable hepatocellular carcinoma lesions, hepatic artery chemoembolization (TACE) is a minimally invasive surgery with the characteristics of low systemic toxicity, strong local effects, and excellent overall efficacy. In a prospective study of 183 patients with hepatocellular carcinoma treated with palliative trans arterial chemoembolization (52 TACE combined with pravastatin and 131 TACE alone), Hannah et al. found that 5-year survival was significantly longer in the combination group (20.9 months, 95% CI 15.5-26.3, p=0.003) [18].

Combined with Targeted Therapy

Sorafenib is a first-line targeted drug for treating advanced hepatocellular carcinoma, which works as a multikinase inhibitor. However, its clinical efficacy is poor, with frequent cases of drug resistance and adverse reactions. The mechanism of sorafenib resistance is complex and unclear, and has been reported to be associated with increased EGFR expression, activation of the c-Jun and Akt pathways in hepatocellular carcinoma cells, EMT activation, increased tumor stem cells, and a hypoxic microenvironment [19]. Anaerobic glycolysis is characteristic of malignant tumor cells, and sorafenib inhibits glycolysis in hepatocellular carcinoma cells [20]. PKM2 is a glycolysis rate-limiting enzyme and is highly expressed in most tumors [21]. Feng et al. found that sorafenib combined with simvastatin could re-sensitize sorafenib-resistant LM3 cell lines to sorafenib, and the specific mechanism might be related to the fact that statin reduces the efficiency of glycolysis inhibits the proliferation of hepatocellular carcinoma cells, and promotes apoptosis of tumor cells by inhibiting the HIF1α/PPAR-γ/PKM2 signaling pathway [22]. As an important cell membrane receptor that recognizes lipopolysaccharide (LPS), TLR4 can activate hepatic stellate cells and promote hepatic fibrosis, in which NF-κB and MAPK are the important conductor proteins downstream of TLR4, which are the key stimulators of hepatocellular carcinoma cell proliferation and apoptosis inhibitors [23]. Yang et al. used sorafenib and fluvastatin to co-treat HepG2 and SK-Hep-1 hepatocellular carcinoma cell lines as well as diethylnitrosamine-induced rat hepatocellular carcinoma models, and found that fluvastatin synergistically inhibited hepatocellular carcinoma cell proliferation and promoted tumor cell apoptosis in vitro and in vivo in a synergistic manner with sorafenib.

The specific mechanism behind this effect may be that statin inhibits the LPS/TLR4-activated NF-κB/MAPK signaling pathway in hepatocellular carcinoma cells [24]. Dasatinib is a potent second-generation BCR-ABL1 tyrosine kinase inhibitor that has been shown to have therapeutic effects on a variety of tumors [25]. EI et al. used rosuvastatin in combination with dasatinib to treat HepG2 hepatocellular carcinoma cell lines and diethylnitrosamine induced mouse hepatocellular carcinoma models. They found that the combination therapy group was more effective in inhibiting tumor cell growth and promoting tumor cell

apoptosis than the single therapy group. The mechanism may be that statin inhibits many target proteins and signaling pathways downstream of VEGF, MMP-9, Survivin, Ras/Raf/ERK, and PI3K/Akt by inhibiting the FAK/Src signaling pathway [26]. Xia et al. found that simvastatin combined with sorafenib/gemfetinib/trametinib more significantly inhibited the proliferation of hepatocellular carcinoma cells, and the mechanism included that statin inhibited the YAP-dependent EGFR/PI3K/PDK1/YAP signaling pathway and inhibited the YAP-independent EGFR signaling pathway [27].

Combined with Other Drugs

Cyclooxygenase 2 (COX2) is widely expressed in malignant tumors and is involved in tumorigenesis and development as well as resistance of tumor cells to chemotherapy. NS-398 is a highly selective COX2 inhibitor, and Sun et al. found that simvastatin synergized with NS-398 to produce stronger antiproliferative and pro-apoptotic effects on hepatocellular carcinoma cells, and the main mechanism was that statin inhibited the NF-κB and Akt pathways and activated the Caspase cascade reaction to promote tumor cell apoptosis [28]. Celecoxib also belongs to the highly selective COX2 inhibitors, Gao et al. used fluvastatin combined with celecoxib in male nude mice xenograft BEL-7402 cell hepatocellular carcinoma model, and found that statin enhanced the anti-tumor ability of celecoxib, and the main mechanism was that statin can inhibit the expression of VEGF to reduce the density of microvessels, up-regulate the expression of cell-cycle protein-dependent kinase inhibitors p21Waf1/Cip1 to inhibit the proliferation of tumors, and down-regulate the expression of Mcl-1 and Survivin to promote the apoptosis of tumor cells [29]. Jian Gao et al. also found in their in vivo studies that fluvastatin can promote tumor cell apoptosis and enhance the anti-tumor ability of celecoxib by inhibiting Akt activation and Survivin expression [30].

Clinical Study on the Prevention and Treatment of Liver Cancer with Statin Drugs

Kim et al. conducted a nationwide nested case-control study by counting the Korean National Health Insurance Service physical examination data from 2002-2013 and found that the risk of hepatocellular carcinoma was significantly decreased in statin users compared with non-users (risk ratio = 0.44, 95% CI = 0.33-0.58) [31]. Tracey et al. conducted a prospective propensity score-matched cohort study of 16,668 adults (6,554 on fat-soluble statins, 1,780 on hydrophilic statins, and 8,334 without statins) in Switzerland from 2005-2013 and found that fat-soluble statins reduced the risk of hepatocellular carcinoma in a time- and dose-dependent manner, whereas this effect was not found for hydrophilic statins, suggesting that fat-soluble statins have a unique preventive effect against hepatocellular carcinoma [32]. Adeel et al. followed 7,248 HCV-infected veterans in the United States for more than 2 years and found that statins increased the rate of virologic response to antiviral therapy, decreased the progression of hepatic fibrosis as well as inhibited the incidence of hepatocellular carcinoma [33]. Goh et al. analyzed 7713 chronic HBV-infected patients in Korea between January 2008 and December 2012 and found that the use of statins was inversely connected with the development of hepatocarcinogenesis [1]. Thrift et al. conducted a retrospective cohort study of 15,422 veterans in the United States who were diagnosed with hepatocellular carcinoma between 2002 and 2016 and found that statins reduced all-cause mortality in patients with hepatocellular carcinoma [34]. Yoshikuni et al. analyzed 734 patients who underwent first-time hepatectomy for hepatocellular carcinoma in Japan from 2003-2013 and found that the recurrence

survival rate was significantly lower in the group taking statins than in the control group (P<0.001), and the complete remission rate was higher than that in the control group (P=0.008) [35]. A prospective cohort study in the United States found that the use of statins is associated with a significant reduction in hepatocellular carcinoma related mortality in patients with non-alcoholic fatty liver disease [36]. A retrospective study in the United States demonstrated that statins significantly reduced the risk of hepatocellular carcinoma in patients with cirrhosis from non-alcoholic steatohepatitis and that this protective effect of statin was dose-dependent [37].

Controversy about Statins against Hepatocellular Carcinoma

An increasing number of basic and clinical studies have shown that statins have a preventive effect on hepatocellular carcinoma, but there are scholars who do not support the above view. Yi et al. followed 400,318 Koreans for an average of 8.4 years, with 1,686 ultimately diagnosed with hepatocellular carcinoma, and found that total cholesterol levels had a strong negative correlation with the risk of hepatocellular carcinoma, and that statins had no preventive effect on hepatocellular carcinoma [38]. Jeon et al. performed a multivariate Cox regression analysis of 1036 patients with stage I or II hepatocellular carcinoma diagnosed between 2007 and 2009 in the United States and found that statins did not improve survival time in patients with early-stage hepatocellular carcinoma [39]. Kazuki et al. used a variety of lipid-lowering drugs fed to STAM mice and found that Rosuvastatin neither inhibited the progression of non-alcoholic steatohepatitis induced by streptozotocin and a high-fat diet in STAM mice, nor reduced the incidence of hepatocellular carcinoma [40].

Summary

In summary, statins can play a tumor-suppressive role in many aspects of hepatocellular carcinoma development. However, more randomized controlled double-blind, multicenter, prospective clinical trials are needed for further evidence. As the prevention of cardiovascular and cerebrovascular first-line drugs, statins or old drugs can be used for new purposes, adding a new highlight for the prevention and treatment of tumors

References

1. Goh MJ, Sinn DH, Kim Set, Paik SW, Lee JH, et al. (2020) Statin Use and the Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B[J]. Hepatology 2020, 71(6):2023-32.
2. Park HS, Jang JE, Ko MS, Koh EH, Lee KU, et al. (2016) Statins Increase Mitochondrial and Peroxisomal Fatty Acid Oxidation in the Liver and Prevent Non-Alcoholic Steatohepatitis in Mice[J]. Diabetes Metab J. 40(5):376-85.
3. Zheng T. (2015) The protective effect and mechanism of atorvastatin on DEN induced hepatitis cirrhosis liver cancer progression in rats [J]. Second Military Medical University 2015.
4. Ridruejo E, Romero-Caími G, Obregón MJ, de Pisarev DK, Alvarez L, et al, (2018) Potential Molecular Targets of Statins in the Prevention of Hepatocarcinogenesis[J]. Ann Hepatol. 17(3):490-500.

5. Wang ST, Ho HJ, Lin JT, Sjieh JJ, Wu CY, et al. (2017) Simvastatin-induced cell cycle arrest through inhibition of STAT3/SKP2 axis and activation of AMPK to promote p27 and p21 accumulation in hepatocellular carcinoma cells[J]. Cell Death Dis. 8(2):e2626.
6. Russell JO, Monga SP. (2018) Wnt/β-Catenin Signaling in Liver Development, Homeostasis, and Pathobiology[J]. Annu Rev Pathol. 13:351-78.
7. Xia K, Zhang P, Hu J, Hou H, Xiong J, et al. (2018) Synergistic effect of receptor-interacting protein 140 and simvastatin on the inhibition of proliferation and survival of hepatocellular carcinoma cells[J]. Oncol Lett. 15(4):4344-50.
8. Wang ST, Huang SW, Liu KT, Lee TU, Shieh JJ, et al. (2020) Atorvastatin-induced senescence of hepatocellular carcinoma is mediated by downregulation of hTERT through the suppression of the IL-6/STAT3 pathway[J]. Cell death discover. 6:17.
9. Relja B, Meder F, Wang M, Blaheta R, Marzi I, et al. (2011) Simvastatin modulates the adhesion and growth of hepatocellular carcinoma cells via decrease of integrin expression and ROCK[J]. Int J Oncol. 38(3):879-85.
10. Taras D, Blanc JF, Rullier A, Dugot-Senant N, Viduad N, et al. (2007) Pravastatin reduces lung metastasis of rat hepatocellular carcinoma via a coordinated decrease of MMP expression and activity[J]. J Hepatol. 46(1):69-76.
11. Salis O, Okuyucu A, Bedir A, Gor U, Kulcu C, et al. (2016) Antimetastatic effect of fluvastatin on breast and hepatocellular carcinoma cells in relation to SGK1 and NDRG1 genes[J]. Tumour biology: the journal of the International Society for Oncodevelopmental Biology and Medicine. Tumour Biol. 37(3):3017-24.
12. Huang X, Ma J, Xu J, Su Q, Zhao J. et al. (2015) Simvastatin induces growth inhibition and apoptosis in HepG2 and Huh7 hepatocellular carcinoma cells via upregulation of Notch1 expression[J]. Mol Med Rep. 11(3):2334-40.
13. Zhang W, Wu J, Zhou L, Xie HY, Zheng SS, et al. (2010) Fluvastatin, a lipophilic statin, induces apoptosis in human hepatocellular carcinoma cells through mitochondria-operated pathway[J]. Indian J Exp Biol. 48(12):1167-74.
14. You HY, Zhang WJ, Xie XM, Zhu HL, Jiang FZ, et al. (2016) Pitavastatin suppressed liver cancer cells in vitro and in vivo[J]. Onco Targets Ther. 9:5383-88.
15. Nishio T, Taura K, Nakamura N, Seo S, Uemto S, et al. (2018) Impact of statin use on the prognosis of patients with hepatocellular carcinoma undergoing liver resection: a subgroup analysis of patients without chronic hepatitis viral infection[J]. Surgery. 163(2):264-69.
16. Cho Y, Kim MS, Nam CM, Kang ES. (2019) Statin Use is Associated with Decreased Hepatocellular Carcinoma Recurrence in Liver Transplant Patients[J]. Sci Rep. 9(1):1467.
17. Guo L, Zheng J, Zeng H, Zhang Z, Shao G, et al. (2021) Atorvastatin potentiates the chemosensitivity of human liver cancer cells to cisplatin via downregulating YAP1[J]. Oncol Lett. 21(2):82.
18. Graf H, Jüngst C, Straub G, Walter A, Jungst D, et al. (2008) Chemoembolization combined with pravastatin improves survival in patients with hepatocellular carcinoma[J]. Digestion. 78(1):34-8.

19. Niu L, Liu L, Yang S Chen GG, Lai PBS, et al. (2017) New insights into sorafenib resistance in hepatocellular carcinoma: Responsible mechanisms and promising strategies[J]. Biochim Biophys Acta Rev Cancer. 1868(2):564-70.
20. Li S, Li J, Dai W, Feng J, Liu T, et al. (2017) Genistein suppresses aerobic glycolysis and induces hepatocellular carcinoma cell death[J]. Br j cancer. 117(10):1518-28.
21. Dong G, Mao Q, Xia W, Xu Y, Wang J, et al. (2016) PKM2 and cancer: The function of PKM2 beyond glycolysis[J]. Oncol Lett. 11(3):1980-86.
22. Feng J, Dai W, Mao Y, Wu L, Li J, et al. (2020) Simvastatin re-sensitizes hepatocellular carcinoma cells to sorafenib by inhibiting HIF-1α/PPAR-γ/PKM2-mediated glycolysis[J]. J Exp Clin Cancer Res. 39(1):24.
23. Peng XX, Zhang SH, Wang XL, Xan Xf, Li H, et al. (2015) Panax Notoginseng flower saponins (PNFS) inhibit LPS-stimulated NO overproduction and iNOS gene overexpression via the suppression of TLR4-mediated MAPK/NF-kappa B signaling pathways in RAW264.7 macrophages[J]. Chin med. 10:15.
24. Cheng Y, Luo R, Zheng H, wang B, Liu D, et al. (2017) Synergistic anti-tumor efficacy of sorafenib and fluvastatin in hepatocellular carcinoma [J]. 8(14):23265-76.
25. Miklja Z, Yadav VN, Cartaxo RT, Siada R, Paul A, et al. Everolimus improves the efficacy of dasatinib in PDGFRα-driven glioma[J]. J Clin Invest. 130(10):5313-25.
26. El Sayed I, Helmy MW, El-Abhar HS, (2018) Inhibition of SRC/FAK cue: A novel pathway for the synergistic effect of rosuvastatin on the anti-cancer effect of dasatinib in hepatocellular carcinoma[J]. Life sci. 213:248-57.
27. Xia H, Dai X, Yu H, Zhou S, Fan Z, et al. (2018) EGFR-PI3K-PDK1 pathway regulates YAP signaling in hepatocellular carcinoma: the mechanism and its implications in targeted therapy[J]. Cell Death Dis. 9(3):269.
28. Lee SJ, Hwang JW, Yim H, Woo SK, Suh SJ, et al. (2014) Synergistic effect of simvastatin plus NS398 on inhibition of proliferation and survival in hepatocellular carcinoma cell line[J]. J Gastroenterol Hepatol. 29(6):1299-1307.
29. Gao J, Jia WD, Li JS, Zhang CH, Wang W, et al. (2010) Combined inhibitory effects of celecoxib and fluvastatin on the growth of human hepatocellular carcinoma xenografts in nude mice[J]. J Int Med Res. 38(4):1413-27.
30. Gao J, Li JS, Xu GL, Wang W, Ren WH, et al. (2010) The effect of celecoxib combined with fluvastatin on the growth and apoptosis of subcutaneous transplanted human liver cancer in nude mice [J]. J Int Med Res. (12):900-04.
31. Kim G, Jang SY, Nam CM, Kang ES. (2018) Statin use and the risk of hepatocellular carcinoma in patients at high risk: A nationwide nested case-control study[J]. J Hepatol. 68(3):476-84.
32. Simon TG, Duberg AS, Aleman S, Hagstrom H, Nguyen LH, et al. (2019) lipophilic Statins and Risk for Hepatocellular Carcinoma and Death in Patients with Chronic Viral Hepatitis: Results From a Nationwide Swedish Population[J]. Ann Intern Med. 171(5):318-27.
33. Butt AA, Yan P, Bonilla H, Shaikh OS, Rogal SS, et al. (2015) Effect of addition of statins to antiviral theraropy in hepatitis C virus-infected persons: Results from ERCHIVES[J]. Hepatology. 62(2):365-74.

34. Thrift AP, Natarajan Y, Liu Y, El-serag HB, et al. (2019) Statin Use After Diagnosis of Hepatocellular Carcinoma Is Associated with Decreased Mortality[J]. Clinical gastroenterology and hepatolog: the official clinical practice. Clin Gastroenterol Hepatol. 17(10):2117-25.
35. Kawaguchi Y, Sakamoto Y, Ito D, Ito K, Arita J, et al. (2017) Statin use is associated with a reduced risk of hepatocellular carcinoma recurrence after initial liver resection[J]. Biosci trends. 11(5):574-80.
36. Hajifathalian K, Tafesh Z, Rosenblatt R, Kumar S, Homan EA, et al. (2022) Effect of Statin Use on Cancer-related Mortality in Nonalcoholic Fatty Liver Disease: A Prospective United States Cohort Study[J]. J Clin Gastroenterol. 56(2):173-80.
37. Pinyopornpanish K, Al-Yaman W, Butler RS, Carey W, Romero-Marrero C, et al. (2021) Chemopreventive Effect of Statin on Hepatocellular Carcinoma in Patients with Nonalcoholic Steatohepatitis Cirrhosis[J]. Am j gastroenterol. 116(11):2258-69.
38. Yi SW, Kim SH, Han KJ, Yi JJ, Ohrr H, et al. (2020) Higher cholesterol levels, not statin use, are associated with a lower risk of hepatocellular carcinoma[J]. Br j cancer. 122(5):630-33.
39. Jeon CY, Goodman MT, Cook-Wiens G, Sundaram V, et al. (2016) Statin Use and Survival with Early-Stage Hepatocellular Carcinoma[J]. Cancer Epidemiol Biomarkers Prev. 25(4):686-92.
40. Orime K, Shirakawa J, Togashi Y, Tajima K, Inoue H, et al. (2016) Lipid-lowering agents inhibit hepatic steatosis in a non-alcoholic steatohepatitis-derived hepatocellular carcinoma mouse model [J]. Eur J Pharmacol. 772:22-32.