

# Antitumor Effects and Mechanisms of Metabolic Syndrome Medications on Hepatocellular Carcinoma

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**Abstract:** Liver cancer has a high incidence and mortality rate worldwide, with hepatocellular carcinoma (HCC) being the most common histological type. With the decrease in the number of newly infected patients and the spread of antiviral therapy, hepatitis virus-negative chronic liver diseases including steatohepatitis are increasingly accounting for a large proportion of HCC, and an important clinical characteristic is the high prevalence of metabolic syndrome including hypertension, type 2 diabetes (T2D), dyslipidemia, and obesity. Since patients with steatohepatitis are less likely to undergo surveillance for early detection of HCC, they may be diagnosed at an advanced stage and have worse prognosis. Therefore, treatment strategies for patients with HCC caused by steatohepatitis, especially in advanced stages, become increasingly important. Further, hypertension, T2D, and dyslipidemia may occur as side effects during systemic treatment, and there will be increasing opportunities to prescribe metabolic syndrome medications, not only for originally comorbid diseases, but also for adverse events during HCC treatment. Interestingly, epidemiological studies have shown that patients taking some metabolic syndrome medications are less likely to develop various types of cancers, including HCC. Basic studies have also shown that these drugs have direct antitumor effects on HCC. In particular, angiotensin II receptor blockers (a drug group for treating hypertension), biguanides (a drug group for treating T2D), and statins (a drug group for treating dyslipidemia) have shown to elucidate antitumor effects against HCC. In this review, we focus on the antitumor effects of metabolic syndrome medications on HCC and their mechanisms based on recent literature. New therapeutic agents are also increasingly being reported. Analysis of the antitumor effects of metabolic syndrome medications on HCC and their mechanisms will be doubly beneficial for HCC patients with metabolic syndrome, and the use of these medications may be a potential strategy against HCC.

**Keywords:** hypertension, angiotensin II receptor blockers, diabetes, biguanide, dyslipidemia, statin

## Introduction

In 2021, liver cancer had the sixth highest incidence and the third highest mortality rate of all cancer types worldwide.<sup>1,2</sup> Hepatocellular carcinoma (HCC) is the most common major histologic type of primary liver cancer, accounting for over 90% of cases.<sup>3</sup> Despite the development of therapeutic modalities, HCC holds one of the poorest cancer prognoses due to the difficulty of early detection, resistance to anticancer drugs, and high recurrence rate, with a 5-year survival rate of 15–38%.<sup>4–6</sup> The occurrence of HCC is strongly related to high hepatitis virus infection rates, including hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. For instance, HBV-induced chronic hepatitis (CH) is the main cause of HCC in China, Southeast Asia, and Central and South Africa, while HCV-induced CH is the main cause of HCC in Japan and Southern Europe.<sup>3</sup> Although the details of association between hepatitis viruses and carcinogenesis are still unclear, clinical data exist to support these findings. HBV carriers are at a higher risk of developing HCC at higher HBV load,<sup>7</sup> while reports show that HCV elimination with interferon or direct-acting antivirals was effective in reducing HCC occurrence.<sup>8,9</sup> Furthermore, HCC is associated with high rates of CH and cirrhosis due to the persistence of neuroinflammatory responses from hepatocytes, a major cause of hepatocarcinogenesis. Multiple factors are intricately involved, including the persistence of immune-mediated inflammation,<sup>10</sup> their associated genetic mutations, and altered

intracellular signaling.<sup>11</sup> However, the occurrence of HCC without cirrhosis is common in the elderly, which may be related to age-related changes in the immune response.

Although most cases of HCC are caused by hepatitis viruses, 5–20% of HCC patients in Japan are negative for both HBV and HCV.<sup>12,13</sup> The major causative factors of HCC are alcoholic liver injury, nonalcoholic fatty liver disease (NAFLD), autoimmune hepatitis, and aflatoxin exposure.<sup>3,14</sup> With declining numbers of new HBV and HCV infections and the widespread use of antiviral therapies, the proportion of HCC caused by hepatitis virus infection has recently been on the decline, whereas the number of hepatocarcinogenesis cases caused by alcoholic or nonalcoholic steatohepatitis (NASH) has been increasing.<sup>15</sup> Our epidemiological study of 802 HCC patients treated in our Department (Kagawa University Hospital, Japan) over a 15-year period from 2003 to 2017 also showed an increase in hepatitis virus-negative HCC including steatohepatitis with the proportion gradually increasing to 11.8% in the early period, 32.9% in the middle period, and 41.1% in the late period.<sup>16</sup> Their important clinical characteristics include a high prevalence of metabolic syndrome, with 47.5% having hypertension, 42.0% having type 2 diabetes (T2D), and 47% having obesity. Furthermore, patients who are not infected with hepatitis virus are less likely to undergo surveillance for early detection of HCC, and therefore may be diagnosed at an advanced stage and have a poorer prognosis. Consequently, treatment strategies for patients with HCC caused by steatohepatitis will become more important, especially for advanced stage cases.

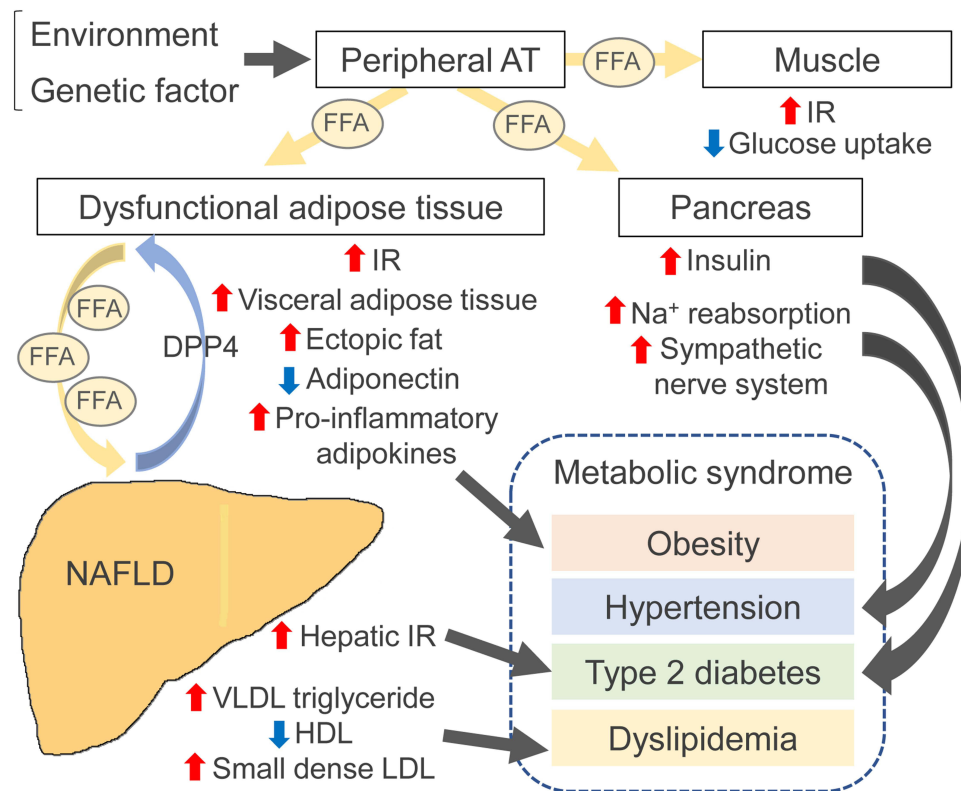
Systemic therapy of advanced HCC that is unresectable due to major vascular invasion and/or metastasis generally involves immune checkpoint inhibitors and molecular targeted agents with several currently available drugs including atezolizumab/bevacizumab combination therapy for first-line therapy and sorafenib, lenvatinib, and other drugs for second-line therapy.<sup>17,18</sup> However, hypertension, T2D, and dyslipidemia may occur as side effects during these systemic therapies; in the future, there will be more opportunities to prescribe metabolic syndrome medications not only for originally comorbid conditions, but also for adverse events during HCC treatment.

Interestingly, epidemiological studies have shown that patients taking several metabolic syndrome medications are less likely to develop various types of cancers.<sup>19–22</sup> There are also basic studies that have showed the direct antitumor effects of metabolic syndrome medications on various cancer cells.<sup>23–28</sup> Analysis of these antitumor effects on HCC and their mechanisms will be doubly beneficial for HCC patients who have metabolic syndrome. Further, preclinical studies and clinical trials suggest that regimens that include therapeutic immunotherapies targeting programmed death-1 (PD1), such as the atorolimumab/bevacizumab combination, may be less effective against NASH-induced HCC,<sup>29,30</sup> and metabolic syndrome drugs may provide adjuvant antitumor effects through an entirely different mechanism. In this review, based on recent literature, we summarize the association between HCC development and metabolic syndrome, including obesity, hypertension, T2D, and dyslipidemia. We also focus on the antitumor effects of various metabolic syndromes on HCC and their mechanisms and discuss their therapeutic applications.

## Obesity and Liver Disease

Obesity is characterized by chronic accumulation of excess body fat caused by genetics, environmental factors, comorbidities, and certain medical treatment such as hormone therapy.<sup>31,32</sup> It was shown that more than 700 million adults, or approximately 15% of all adults worldwide, were obese in 2020, and the number is expected to increase rapidly.<sup>32</sup> Obesity is an independent risk factor for progression of many diseases, including T2D, cardiovascular disease, hypertension, dyslipidemia, and NAFLD.<sup>31</sup> Recent reports have also linked it to an increased risk of various cancers, including HCC.<sup>33</sup> The pathophysiology of NAFLD can lead to HCC development not caused by the hepatitis virus, on the continuum to metabolic syndrome, including hypertension, diabetes, dyslipidemia, and obesity is shown in [Figure 1](#).<sup>34</sup> NAFLD progresses to NASH characterized by hepatocyte ballooning, apoptosis, accumulation of Mallory–Denk bodies, and inflammation in the liver parenchyma and portal vein and ultimately leads to irreversible cirrhosis and hepatocellular carcinogenesis.

While treatment for obesity and related chronic liver disease primarily consists of lifestyle modifications focused on weight management, patients with moderate to severe obesity or mild obesity refractory to lifestyle therapy should be considered for pharmacotherapy. Orlistat is a gastrointestinal lipase inhibitor that modestly reduces body weight by limiting the absorption of fat from the intestinal tract, but has been shown to reduce intrahepatic inflammation and fibrosis in steatohepatitis.<sup>35</sup> Combination weight-reduction therapies, including phentermine/topiramate and naltrexone-bupropion do not show a preventive effect on HCC, but may be of clinical value because weight reduction is associated



**Figure 1** Pathophysiology of nonalcoholic fatty liver disease (NAFLD) on the continuum to metabolic syndrome. When environmental and genetic factors induce weight gain, increased mobilization of free fatty acids (FFAs) from subcutaneous adipose tissue (AT) results in accumulation of visceral and ectopic fat. In the muscle, increased accumulation of FFAs promotes insulin resistance (IR) and inhibits insulin-mediated glucose uptake. FFAs leaking into the pancreas cause  $\beta$ -cell dysfunction and hyperglycemia. Insulin resistance (IR) promotes lipolysis in dysfunctional AT and increases the flux of FFAs to the liver, promoting hepatic glucose production, lipogenesis, release of very low-density lipoproteins (VLDLs), and dyslipidemia. These global IR conditions can lead to hyperinsulinemia; they promote sodium reabsorption and lead to hypertension. Inflamed dysfunctional AT increases IR and releases levels of inflammatory adipokines while decreasing anti-inflammatory adiponectin levels. In the liver, triglycerides and toxic metabolites induce lipotoxicity, mitochondrial dysfunction, and endoplasmic reticulum stress, leading to hepatocyte damage, apoptosis, and fibrosis. These dysfunctional hepatocytes synthesize and secrete dipeptidyl peptidase 4 (DPP4), which promotes AT macrophage inflammation and further causes IR.

with a decrease in intrahepatic lipid accumulation. Liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist used in the treatment of T2D, helps obese patients lose weight by reducing food intake. Liraglutide prevents progression from NAFLD to HCC occurrence in mice with obesity and streptozotocin-induced diabetes.<sup>36</sup> Promising therapeutic approaches target adiposity, hepatitis, and fibrosis through multiple mechanisms of action, such as GLP-1, glucagon receptor, and glucose-dependent insulinotropic polypeptide. There is limited evidence to conclude whether pharmacological treatment of obesity prevents HCC; further preclinical studies and clinical trials on humans are warranted to validate its role in the prevention of hepatocarcinogenesis.

## Hypertension and Liver Disease

Hypertension is one of the major diseases in the metabolic syndrome, along with T2D, dyslipidemia, and obesity, and it affects approximately 30% of the general population. It results from a combination of multiple factors, including genetic predisposition and environmental risk factors such as excessive salt intake, obesity, smoking, lack of exercise, and stress.<sup>37</sup> Hypertension can not only cause ischemic heart disease and cerebrovascular disease, but it is also associated with NAFLD, which encompasses a continuous spectrum leading to NASH with advanced cirrhosis and HCC. Approximately 49.5% of hypertensive patients have NAFLD, indicating a significantly higher prevalence of hypertension in NAFLD patients compared to general population.<sup>38,39</sup> Several prospective studies have also shown that NAFLD is an independent risk factor for the development of hypertension after adjustment for T2D, dyslipidemia, obesity, and other systemic metabolic disorders.<sup>38,40,41</sup> Interestingly, another report has shown that persistence of NAFLD over a 5-year observation period increased the risk of developing hypertension. Meanwhile, the occurrence of hypertension is not

increased in cases with improved imaging findings of fatty liver.<sup>42</sup> It is unclear from the clinical evidence whether NAFLD is a consequence or a cause of hypertension.

Furthermore, it has been shown that NAFLD causes several effects such as hepatitis, insulin resistance, and renin-angiotensin system (RAS)-sympathetic nervous system (SNS) activation, which have been shown to be important physiological mechanisms that lead to hypertension.<sup>43,44</sup> In patients with NAFLD, cardiac and autonomic functions are significantly impaired, independent of SNS, and blood levels of tumor necrosis factor (TNF)- $\alpha$  and cytokeratin 18, which are markers of liver damage, are elevated; therefore, activation of the RAS is shown to be a major mechanism for the progression of hypertension.<sup>45</sup> Via the production of angiotensinogen in the liver and kidney, cytokines such as TNF- $\alpha$  also promote systemic and local angiotensin (Ang) II production and Ang II-dependent hypertension.<sup>46</sup> In addition, several cytokines, such as retinol binding protein 4 and fetuin A, are upregulated in patients with NAFLD, and have been optimized to cause hepatitis by activating toll-like receptor (TLR)-4 dependent inflammatory pathways.<sup>47</sup> However, TLR4 activation can also promote cardiovascular and renal pro-inflammatory cytokines and reactive oxygen species, which may adversely affect hypertension.<sup>48</sup> Furthermore, another report suggests that NAFLD is independently related to the development of chronic liver disease; local kidney inflammation appears to cause hypertension.<sup>49</sup>

In general, blood pressure is often low in the terminal stages of cirrhosis via hemodynamic and blood bioactive substances, but in other cases of chronic liver diseases complicated by hypertension, the usual antihypertensive drugs are used. In patients with severe hepatic dysfunction, blood levels of antihypertensive drugs in hepatic metabolism are increased, necessitating dose reduction. Non-selective  $\beta$ -blockers, such as propranolol, decrease portal blood pressure and reduce the incidence of gastrointestinal bleeding and the risk of death in patients with cirrhosis.<sup>50</sup> RAS inhibitors, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), have the potential to reduce liver fibrosis during the transition from CH to cirrhosis.<sup>51</sup> Other studies showed that RAS inhibitors are effective in improving pathophysiological responses, including liver fibrosis in patients with NAFLD;<sup>52,53</sup> therefore, RAS inhibitors may be best suited as antihypertensive agents for patients with chronic liver disease, especially NAFLD.

## Prevention of HCC Occurrence with Antihypertensive Drugs

Since obesity and NAFLD promote hypertension and affect carcinogenesis, hypertension itself is suggested to have no independent role in the development and progression of HCC; however, there is evidence for preventive and antitumor effects of hypertensive drugs against HCC, independent of their effect on blood pressure. In recent years, there has been a growing number of clinical studies that have examined the association between the risk of HCC development and antihypertensive drugs, such as RAS inhibitors and  $\beta$ -blockers (Table 1). Recent systematic reviews suggest that RAS inhibitors alone or in combination significantly reduce HCC recurrence, although they do not prolong patient survival.<sup>54</sup> Although a case-control study examining the association between RAS inhibitor use and the development of HCC found no significant findings overall, a woman receiving 30 or more cumulative defined daily doses (cDDD) of RAS inhibitors had a significantly lower incidence of HCC in a subgroup analysis.<sup>55</sup> Furthermore, patients without T2D and with RAS inhibitor cDDD of 1800 or higher had significantly reduced the development of HCC compared to those with no RAS inhibitor exposure; this suggests that the risk of HCC occurrence may be lower with higher cumulative doses. Other reports found positive results in patients receiving therapeutic interventions for HCC: it was shown that overall survival (OS) in HCC patients treated with sorafenib and RAS inhibitors was prolonged.<sup>56</sup> HCC patients treated with radiofrequency ablation (RFA) also reported significantly longer OS and disease-free survival in cases that had received ARBs in the previous two years at least, while those treated with ACE inhibitors did not.<sup>57</sup> On the other hand, there are several studies showing negative results regarding the effect of RAS inhibitors in preventing the development of HCC.<sup>58-61</sup> Interestingly, the use of RAS inhibitors rather increased the HCC occurrence in HCV-infected patients without cirrhosis, T2D, or dyslipidemia.<sup>58</sup> In a study of post-tumor resection of HCV-related HCC patients, the ARB-treated group did not have an OS advantage over the control groups, but cirrhosis patients prescribed other antihypertensive drugs had a significantly shorter OS than those prescribed ARB.<sup>61</sup> Several interventional studies examined the effects of ACE inhibitors alone or in combination with other drugs in patients after RFA; these showed that ACE inhibitors reduced the risk of HCC recurrence in combination with branched-chain amino acids (BCAAs) or vitamin K, but no significant OS benefit was observed.<sup>62-64</sup> Thus, although the results for patient survival with RAS inhibitors appear to be contradictory, this accumulating evidence suggests that RAS inhibitors may work to reduce the occurrence of HCC.

**Table 1** Clinical Studies on the Prevention of Hepatocellular Carcinoma (HCC) by Antihypertensive Drugs

<b>Studies on RAS Inhibitors</b>			
<b>Authors (Year)</b>	<b>Design</b>	<b>Patients</b>	<b>Interpretation</b>
Kim et al <sup>55</sup> (2021)	Case-control	Patients newly diagnosed with HCC	RAS inhibitors did not reduce HCC occurrence.
Pinter et al <sup>56</sup> (2017)	Retrospective Cohort	HCC patients received sorafenib treatment	RAS inhibitors significantly prolonged survival.
Facciorusso et al <sup>57</sup> (2015)	Retrospective Cohort	Patients after RFA for HCC	ARB significantly prolonged OS and DFS, while ACE-I did not.
Ho et al <sup>58</sup> (2018)	Retrospective Cohort	Hypertensive patients with HBV or HCV infection	RAS inhibitors did not suppress HCC development.
Herberg et al <sup>45</sup> (2016)	Case-control	Patients who was newly diagnosed with HCC	RAS inhibitors did not reduce HCC occurrence.
Walker et al <sup>60</sup> (2011)	Case-control	Patients who was newly diagnosed with HCC	RAS inhibitors did not reduce HCC occurrence.
Kabori et al <sup>61</sup> (2011)	Retrospective Cohort	Patients after resection for HCC	ARBs prolonged both OS and DFS in hypertensive patients.
Yoshiji et al <sup>62</sup> (2009)	RCT	Patients after curative treatment for HCC	ACE-I / vitamin K suppressed VEGF-mediated neovascularization.
Yoshiji et al <sup>63</sup> (2011)	RCT	Patients after curative treatment for HCC	ACE-I / vitamin K suppressed VEGF-mediated neovascularization.
Yoshiji et al <sup>64</sup> (2011)	RCT	Patients after curative treatment for HCC	ACE-I / BCAA effected anti-angiogenesis.
<b>Studies on <math>\beta</math>-blockers</b>			
<b>Authors (year)</b>	<b>Design</b>	<b>Patients</b>	<b>Interpretation</b>
Udumyan et al <sup>65</sup> (2020)	Retrospective Cohort	Patients newly diagnosed with HCC	$\beta$ -blockers, especially non-selective drugs, reduced HCC mortality.
Nkontchou et al <sup>66</sup> (2012)	Retrospective Cohort	Patients with HCV-related cirrhosis	Propranolol use significantly reduced HCC occurrence.
Suna et al <sup>67</sup> (2019)	Retrospective Cohort	Patients waiting for liver transplant with cirrhosis	Propranolol use significantly reduced HCC occurrence.
Chang et al <sup>68</sup> (2019)	Case-control	Patients with unresectable/metastatic HCC	Propranolol use significantly reduced the mortality risk.
Kim et al <sup>69</sup> (2012)	Retrospective Cohort	Patients with cirrhosis of any cause	Propranolol use prolonged neither OS nor HCC-free survival.

**Abbreviations:** RAS, renin-angiotensin system; RFA, radiofrequency ablation; ARB, angiotensin receptor blocker; OS, overall survival; DFS, disease-free survival; ACE-I, angiotensin converting enzyme inhibitor; HBV, hepatitis B virus; HCV, hepatitis C virus; RCT, randomized controlled trial; VEGF, vascular endothelial growth factor; BCAA, branched-chain amino acid.

There are some remarkable studies on whether the use of  $\beta$ -blockers benefits patients after HCC treatment or puts them at a high risk of carcinogenesis. In a large cohort study,  $\beta$ -blocker use reduced mortality from HCC, and a greater inverse correlation was observed, especially with respect to non-selective  $\beta$ -blocker use.<sup>65</sup> In a retrospective long-term observation study, propranolol treatment was the only independent prognostic factor associated with the HCC development in patients with HCV-related cirrhosis and esophageal varices.<sup>66</sup> Another cohort study of patients with uncompensated cirrhosis awaiting liver transplantation found that the cause and stages of cirrhosis were similar in the propranolol-treated and control groups, but the HCC occurrence was significantly reduced in the propranolol-treated patients. This result supported the fact that propranolol treatment prevented the development of HCC in patients awaiting liver transplantation.<sup>67</sup> In a study investigating the long-term prognosis of patients with unresectable HCC, propranolol was found to significantly reduce mortality risk by 22% and improve OS after performing a multivariate Cox regression analysis on HCC mortality.<sup>68</sup> Conversely, another study showed that a low dose of propranolol in patients with cirrhosis did not make a significant difference in HCC development and

OS.<sup>69</sup> This evidence regarding the prevention of HCC by  $\beta$ -blockers may not only reflect its direct antitumor effect, but could result from an improvement in portal hypertension; caution should be exercised in interpreting these results.

## Antitumor Effects and Mechanisms of RAS Inhibitors on HCC

In recent years, several experimental data have been presented examining the antitumor effects of RAS inhibitors, including ARBs and ACE inhibitors, on HCC (Table 2). In our previous study, we evaluated the antitumor effects of

**Table 2** Experimental Studies on the Antitumor Effects of Renin-Angiotensin System (RAS) Inhibitors Against Hepatocellular Carcinoma (HCC)

Studies on ACE Inhibitors			
Authors (Year)	Model	Drugs	Results
Yoshiji et al <sup>75</sup> (2002)	Endothelial culture Xenograft mice	Perindopril	Activation form of perindopril inhibited VEGF-induced endothelial cell migration in vitro. Perindopril attenuated VEGF-mediated HCC development suppressing neovascularization
Yoshiji et al <sup>76</sup> (2001)	Mouse HCC cell line Xenograft mice	Perindopril and Captopril	Activation form of perindopril suppressed VEGF mRNA expression in vitro. Prindpril and captopril suppressed VEGF level in the tumor
Noguchi et al <sup>78</sup> (2003)	Xenograft mice	Perindopril	Combination treatment of perindopril and IFN- $\beta$ inhibit HCC development and angiogenesis suppressing VEGF expression
Yoshili et al <sup>87</sup> (2006)	Xenograft mice DEN-induced HCC mice	Perindopril	Combination treatment of perindopril and vitamin K inhibit HCC development and angiogenesis suppressing VEGF expression
Yanase et al <sup>84</sup> (2007)	Xenograft mice DEN-induced HCC rats	Perindopril	The combined administration of perindopril and 5-FU reduced the expression of VEGF and showed antitumor effect
Yoshiji et al <sup>77</sup> (2010)	Obese diabetic rats	Perindopril	Perindopril inhibited both angiogenesis and VEGF as well as development of HCC precursor lesions, and showed stronger antitumor effects when combined with BCAAs
Noguchi et al <sup>79</sup> (2013)	NASH-induced rats	Perindopril and eplerenone	Combination treatment with CDAA diet inhibited development of liver fibrosis and pre-neoplastic lesion with suppression of activated hepatic stellate cells and neovascularization
Saber et al <sup>80</sup> (2018)	DEN-induced HCC mice	Perindopril and fosinopril	ACE inhibitors improved liver function and malignant histologic features, and only perindopril reduced AFP levels as well as sorafenib
Saber et al <sup>81</sup> (2018)	DEN-induced HCC mice	Perindopril and fosinopril	ACE inhibitors administered alone or in combination with sorafenib improved malignant histologic features in the liver
Nasr et al <sup>83</sup> (2014)	DEN-induced HCC mice	Perindopril	In combination with leflunomide and curcumin, perindopril inhibited angiogenesis and showed a beneficial histopathologic preventive effect
Yoshiji et al <sup>88</sup> (2005)	DEN-induced HCC rats	Perindopril	Combination treatment of perindopril and vitamin K inhibit HCC development and angiogenesis suppressing VEGF expression
Yoshiji et al <sup>89</sup> (2005)	DEN-induced HCC rats	Perindopril	Combination treatment of perindopril and IFN- $\beta$ suppress VEGF expression and nearly halt the HCC development
Mansour et al <sup>82</sup> (2011)	DEN-induced HCC rats	Captopril and perindopril	ACE inhibitors had protective effects against the precancerous HCC

(Continued)

Table 2 (Continued).

Studies on ARBs			
Authors (year)	Model	Drugs	Results
Oura et al <sup>70</sup> (2017)	HCC cell lines	Telmisartan, valsartan, irbesartan, and losartan	Only telmisartan showed antitumor effects against HLF, HLE, and HepG2 leading activation of AMPK and inhibition of mTOR
Santhekadur et al <sup>71</sup> (2014)	HCC cell lines	Losartan	Losartan inhibited migration and invasion of Hep3B and QGY-7703
Cook et al <sup>72</sup> (2001)	Rat hepatoma cell line	Losartan and candesartan	Only losartan inhibited in competing with angiotensin II / AT1R interactions
Fan et al <sup>73</sup> (2016)	HCC cell lines Xenograft mice	Candesartan	Candesartan did not show antitumor effects on LO2, SMMG7721 and HepG2. Candesartan suppressed tumor growth in xenograft models by decreasing VEGF-A expression
Tamaki et al <sup>74</sup> (2013)	NASH induced rats	Telmisartan	Telmisartan treatment with CDAA diet suppressed hepatocarcinogenesis by decreasing HIF- $\alpha$ and VEGF levels
Saber et al <sup>80</sup> (2018)	DEN-induced HCC mice	Losartan	Losartan administered alone or in combination with sorafenib improved malignant histologic features in the liver
Saber et al <sup>81</sup> (2018)	DEN-induced HCC mice	Losartan	Losartan improved liver function and malignant histologic features
Mansour et al <sup>82</sup> (2011)	DEN-induced HCC rats	Losartan	Losartan had protective effects against the precancerous HCC

**Abbreviations:** ACE, angiotensin converting enzyme; VEGF, vascular endothelial growth factor; DEN, diethylnitrosamine; IFN, interferon; 5-FU, 5-fluorouracil; CDAA, choline-deficient (L)-amino acid-defined; AFP, alpha-fetoprotein; AMPK, AMP-activated protein kinase; mTOR, mammalian target of rapamycin; AT1R, angiotensin II type I receptor; NASH, nonalcoholic steatohepatitis.

several ARBs, including telmisartan, valsartan, irbesartan, and losartan, on HCC using cell lines.<sup>70</sup> Only telmisartan showed antitumor effects on poorly differentiated HCC cell lines, such as HLE, HLF, and HepG2, but not on HuH-7 and PLC/PRF/5. The main mechanism of the antitumor effect was activation of AMP-activated protein kinase (AMPK) and inhibition of mammalian target of rapamycin (mTOR) pathway, resulting in decreased expression of cyclin D1 and G1 arrest.<sup>70</sup> Earlier studies have shown that staphylococcal nuclease domain containing-1 (SND1), known to promote tumorigenesis of HCC cells, increases Ang II type 1 receptor (AT1R) levels. Furthermore, losartan suppressed the migration and invasion of Hep3B and QGY-7703, suggesting that SND1 inhibitors and ARBs may be an effective therapeutic strategy against advanced HCC.<sup>71</sup> In a study using the rat hepatoma cell line, which were transfected with a plasmid producing non-secreted angiotensinogen, losartan inhibited cell growth.<sup>72</sup> Candesartan was as effective as losartan in competing with Ang II-AT1R interactions, but did not inhibit cell growth. These in vitro data can be conflicting, but studies using animal models can help clarify the antitumor effects and mechanisms of ARBs. For example, a study examining the antitumor effects both in vitro and in vivo showed that candesartan did not affect the growth of HCC cell lines including LO2, SMMG7721, and HepG2, while in a xenograft mouse model with SMMG7721, candesartan showed tumor suppression by decreasing the expression of vascular endothelial growth factor (VEGF)-A.<sup>73</sup> Using an animal model of Wistar male rats fed with a 24-week choline-deficient, L-amino acid-defined (CDAA) diet to induce liver cirrhosis and liver carcinogenesis, another author found that telmisartan treatment suppressed liver carcinogenesis by reducing HIF- $\alpha$  and VEGF expression.<sup>74</sup>

The antitumor effects of ACE inhibitors have been validated by several animal experiments. Using xenograft mice models with HCC cell lines, perindopril was found to significantly attenuate VEGF-mediated tumor development suppressing neovascularization at a clinically comparable low dose.<sup>75,76</sup> The same authors also used obese, diabetic

rats treated with dimethylnitrosamine and found that perindopril inhibited both angiogenesis and VEGF expression, as well as the development of HCC precursor lesions, and showed stronger antitumor effects when combined with BCAAs.<sup>77</sup>

The combination of ACE inhibitors with other angiogenesis-related drugs has often been used to enhance antitumor effects against HCC. Combined administration of perindopril and interferon (IFN)- $\beta$  at clinically equivalent low doses in xenograft mice with HCC cell lines has been shown to inhibit HCC development and angiogenesis by suppressing VEGF expression.<sup>78</sup> Using male Fisher-344 rats receiving a modified choline-deficient, low-methionine diet, the same authors also showed that combination treatment with perindopril and eplerenone inhibited development of liver fibrosis and pre-neoplastic lesion with suppression of activated hepatic stellate cells and neovascularization.<sup>79</sup>

Furthermore, previous basic studies using animal models of diethylnitrosamine (DEN)-induced hepatocarcinogenesis also support the evidence associated with premalignant changes of RAS inhibitors on HCC. A study comparing the effects of RAS inhibitors, including perindopril, fosinopril, and losartan, on DEN-induced HCC in mice with standard therapy using sorafenib showed that RAS inhibitors improved liver function and malignant histologic features, while perindopril or sorafenib reduced alpha-fetoprotein (AFP) levels.<sup>80</sup> The main mechanisms of these were through inactivation of the NF $\kappa$ B pathway, which induced TNF- $\alpha$  and reduced transforming growth factor (TGF)- $\beta$ 1 levels, leading to lower VEGF and matrix metalloproteinase (MMP)-2 levels. However, in another study, the same authors reported that perindopril, fosinopril, and losartan, administered alone or in combination with sorafenib, markedly improved liver tissue in DEN-induced HCC mice, but were not associated with prolonged OS due to the adverse effects of DEN on other organs. They concluded that HCC mortality assessment in such animal models may be unsuitable.<sup>81</sup> Animal studies in rats with DEN-induced HCC suggest that RAS inhibitors, including captopril, perindopril, and losartan, have similar protective effects against the precancerous stages of HCC.<sup>82</sup> Treatment of captopril or losartan caused a remarkable decrease in AFP levels and nearly halved VEGF, TGF- $\beta$ , and fibroblast growth factor levels, only in rats with accelerated hepatocarcinogenesis. Another group focused on the antitumor effects by combinations of angiogenesis inhibitors on HCC and reported that, when combining perindopril, leflunomide, and curcumin, the active principle of turmeric more potently inhibited angiogenesis and showed a beneficial histopathologic preventive effect against DEN-induced HCC in mice.<sup>83</sup> As an effective therapeutic strategy, the combination of angiogenesis inhibitors with conventional chemotherapeutic agents provides synergistic anticancer effects. Although perindopril and 5-fluorouracil (5-FU) did not have a significant inhibitory effect on HCC growth when used at low doses, their combined administration reduced the expression of VEGF and suppressed tumor growth in xenograft mice with BNL-HCC cells.<sup>84</sup> Furthermore, even in DEN-treated rats, this combination treatment markedly suppressed the development of precancerous HCC lesions.

Furthermore, Vitamin K is a comprehensive drug that has been shown to have antitumor effects against HCC,<sup>85,86</sup> and, in combination with perindopril, has inhibited tumor growth in xenograft mice with HCC cells and inhibited hepatocarcinogenesis in DEN-induced HCC mice and rats.<sup>87,88</sup> The same authors also reported that perindopril, when used in combination with IFN- $\beta$ , could suppress VEGF expression and nearly halt HCC development in DEN-induced rats.<sup>89</sup> These reports suggest that ACE inhibitors may exert stronger antitumor effects in combination with other angiogenesis inhibitors or standard treatments for HCC, which may provide clues for therapeutic applications.

## Type 2 Diabetes (T2D) and Liver Disease

T2D is characterized by a disruption of glucose homeostasis and defective insulin action in many target tissues, including the liver, muscles, and pancreas.<sup>90</sup> T2D affects 1 in 11 adults, or 463 million people, globally.<sup>91</sup> Patients with T2D are at more than twice the risk of progressive fibrosis, cirrhosis-related complications, and liver disease mortality compared to individuals without T2D. Furthermore, these patients show higher risk of severe liver diseases than patients with any other diseases, including obesity, hypertension, and dyslipidemia.<sup>92</sup> A longer history of metabolic dysfunction has been shown to be related to more progressive liver fibrosis in NAFLD patients.<sup>93</sup> In turn, NAFLD patients are more likely to have T2D, which is caused by insulin resistance and damaged islet cell function.<sup>91</sup> Individuals diagnosed with NAFLD have a two-fold higher risk of T2D<sup>94</sup> and a higher risk of developing cardiovascular disease<sup>95,96</sup> and hepatocarcinogenesis,<sup>97</sup> especially when associated with T2D.



In clinical studies investigating the risk factor of cancers in patients with T2D, elevated levels of the potent mitogen insulin-like growth factor (IGF)-1 have been reported, which may contribute to cancer development.<sup>98</sup> In addition, an association between T2D and carcinogenesis has been suggested in several organs such as the endometrium, breast, pancreas, liver, stomach, and liver.<sup>99</sup> For instance, the risk of biliary tract cancer is increased in patients with T2D,<sup>100</sup> while the prevalence of prostate cancer is decreased in patients with T2D.<sup>101</sup> T2D is often accompanied by dyslipidemia and obesity, which further increases the risk of cancer development, especially of most site-specific cancers.<sup>102</sup> A strong positive correlation with endometrial and renal cancers was reported, while a weak one with bladder, prostate, and stomach cancers was reported.<sup>103,104</sup> Interestingly, the incidence of lung cancer was inversely correlated with T2D and obesity.<sup>103</sup> T2D is also closely associated with the prevalence of HCC. Studies in diverse populations with T2D have reported that T2D increases the HCC occurrence by two to three times; the risk of HCC was significantly higher in males than in females.<sup>105</sup> Furthermore, the risk of HCC may increase with a longer duration of T2D,<sup>106</sup> but the association between T2D severity and the HCC occurrence remains unknown.

In T2D patients, insulin resistance and hyperinsulinemia are important mechanisms of liver disease progression. As the T2D progresses, chronic hyperglycemia and failure of peripheral tissues to respond to circulating insulin leads to insulin resistance. Hyperinsulinemia caused by impaired glucose metabolism of insulin in the skeletal muscle and the liver increases the production of IGF-1 and promotes hepatocyte proliferation and inhibition of apoptosis.<sup>107</sup> In addition, insulin resistance and hyperinsulinemia have been reported to be closely associated with the development of HCC resulting from NAFLD.<sup>108</sup> Among other factors in the pathogenesis of T2D, inflammatory cytokines,<sup>109</sup> oxidative stress,<sup>110</sup> gut microbiota abnormalities,<sup>111,112</sup> angiogenesis,<sup>113</sup> and autophagy<sup>114</sup> influence development and progression of HCC.

## Suppression of HCC Occurrence by T2D Medication

Several T2D drugs associated with cancer have been reported. As noted above, insulin has tumor growth effects, and the use of insulin secretagogues and insulin preparation may increase the risk of cancer. The use of sulfonylureas (SU), insulin secretagogues, increased the risk of cancer,<sup>115</sup> with a reported cancer risk being 1.78 times higher in SU users than in metformin users.<sup>116</sup> Research results on insulin preparations and cancer risk have been inconsistent, with past studies reporting an increase in cancer risk, specifically in breast cancer among insulin glargine users,<sup>117,118</sup> while others have found no association.<sup>119</sup> Addressing the limitations and biases of previous studies, a recent study found that there appear to be differences in cancer risk by cancer type and duration of treatment.<sup>120</sup> Specifically in liver cancer, the study had shown a lower risk of carcinogenesis in men who had been treated with insulin for three to four years.<sup>120</sup>

Of the oral glucose-lowering drugs, metformin most commonly affects the incidence of HCC (Table 3). In a pioneering study, metformin use was associated with decreased cancer risk, reporting an odds ratio of 0.86 (95% confidence interval (CI): 0.73–1.02) for cancer occurrence.<sup>121</sup> Regarding HCC occurrence, a retrospective case-control study including 610 HCC patients, 618 cirrhosis patients, and 1696 controls reported that metformin use was related to the lower risk of HCC occurrence compared with SU or insulin use.<sup>122</sup> Another hospital-based study including 420 HCC patients and 1104 controls reported that SU or insulin use was associated with the highest risk for HCC occurrence, while metformin or glitazone use reduced HCC risk by 70% in patients with T2D.<sup>123</sup> In addition, in a large cohort study including 19,349 diabetes patients and 77,396 controls, patients with T2D had a two-fold higher incidence of HCC than controls, and those treated with either metformin or glitazone had a significantly lower incidence of HCC than those treated with other drugs.<sup>124</sup> Several recent meta-analyses support these results. In one consisting of five case-control studies, three cohort studies, and two randomized controlled trials (RCTs), it was shown that patients treated with metformin had approximately 50% less HCC occurrence than those treated with SU, glitazone, or insulin.<sup>125</sup> In another meta-analysis including one RCT, four cohort studies, and eight case-control studies enrolling approximately 480,000 T2D patients, metformin use decreased the risk of HCC incidence, and interestingly, insulin use was conversely associated with an increased risk of HCC occurrence.<sup>126</sup> It should be noted, however, that there have been conflicting results from an observational study showing no association between the use of hypoglycemic drugs, including metformin, and incidence of all cancers, including HCC.<sup>127</sup> How metformin decreases the risk of HCC development remains unclear, and larger RCTs are needed.

**Table 3** Clinical Studies on the Prevention of Hepatocellular Carcinoma (HCC) by Metformin

Authors (Year)	Design	Patients	Interpretation
Evans et al <sup>121</sup> (2005)	Retrospective Cohort	Patients who was newly diagnosed with T2D	Metformin use significantly reduce HCC risk in patients with T2D.
Donadon et al <sup>122</sup> (2010)	Case-control	Patients who was newly diagnosed with HCC	Metformin use reduce HCC occurrence compared to SU and insulin.
Hassan et al <sup>123</sup> (2011)	Case-control	Patients who was newly diagnosed with HCC	Metformin or glitazone use reduce HCC risk by 70% in patients with T2D.
Lai et al <sup>124</sup> (2012)	Retrospective Cohort	Patients who was newly diagnosed with T2D	Metformin or glitazone use significantly reduce HCC risk in patients with T2D.
Singh et al <sup>125</sup> (2013)	Meta-analysis	Patients under treatment for T2D	Metformin use reduce HCC risk by 50% in patients with T2D.
Tsilidis et al <sup>127</sup> (2014)	Retrospective Cohort	Patients who was newly diagnosed with T2D	Metformin user had similar incidence rates of HCC.
Zhou et al <sup>126</sup> (2016)	Meta-analysis	Patients under treatment for T2D	Metformin use was associated with a decreased risk of HCC occurrence.

**Abbreviation:** T2D, type 2 diabetes.

Dipeptidyl peptidase-4 (DPP-4) has seen a rapid expansion in clinical use over the past decade, which acts by lowering blood glucose by inhibiting the degradation of incretin.<sup>128,129</sup> Cases presenting inhibition of DPP-4 show elevated levels of both endogenous glucose-dependent insulinotropic polypeptide-1 (GLP-1) and GLP-2, which play crucial roles in cancer progression and metastasis.<sup>130</sup> Though the appropriateness of long-term DPP-4 inhibitor use is debatable, some studies suggest that diabetic patients treated with DPP-4 inhibitors do not have a higher risk of cancer development than those treated with placebo or other drugs.<sup>131,132</sup> Although there is not much epidemiologic evidence on the risk of developing HCC, one study, comparing the risk of HCC in adults with T2D and HCV-related CH who received DPP-4 inhibitor therapy versus those who did not, showed that DPP-4 inhibitor use suppressed the HCC occurrence.<sup>133</sup> In a cohort study of propensity score-matched DPP-4 inhibitor users and non-users in patients with compensated liver cirrhosis, DPP-4 inhibitor use caused the development of decompensated cirrhosis and hepatic failure.<sup>134</sup>

Sodium/glucose cotransporter-2 (SGLT-2) is a protein involved in glucose reabsorption in the renal tubules. SGLT-2 inhibitors are effective against T2D<sup>135</sup> which selectively inhibit renal glucose reabsorption, thereby increasing urinary glucose excretion and lowering plasma glucose levels.<sup>136</sup> A meta-analysis based on evidence from short-term RCTs showed that SGLT2 inhibitors did not significantly increase overall cancer risk compared to placebo or other drugs.<sup>137</sup> However, empagliflozin may increase the risk of bladder cancer and canagliflozin may decrease the risk of gastrointestinal cancers.<sup>137</sup> In another meta-analysis incorporating 27 clinical trials, use of SGLT-2 inhibitors did not increase the risk of developing any common malignancies, including prostate, skin, breast, gastrointestinal tract, bladder, respiratory airways, kidney, pancreas, female genital tract, and liver cancer.<sup>138</sup> Although there are no ongoing clinical trials on the use of SGLT-2 inhibitors in HCC patients, there are several clinical trials of SGLT-2 inhibitors in NASH that are expected to shed further light on its potential clinical benefit in patients with NASH-associated HCC.<sup>139–141</sup>

## Antitumor Effects and Mechanism of T2D Drugs on HCC

Metformin is not only suggested to have cancer-inhibitory effects in many cohort and case-control studies, but it is also the T2D drug whose antitumor mechanisms have been most investigated in basic and animal studies in recent years. In general, the antitumor effects of metformin are assumed to be mediated by mechanisms such as activating AMPK, suppressing mammalian target of rapamycin (mTOR), inhibiting human epithelial growth factor receptor 2 (HER2) expression, suppressing angiogenesis, arresting the cell cycle, and inducing apoptosis.<sup>142</sup> Several basic studies have demonstrated a variety of antitumor effects, including direct inhibition of tumor growth and induction of apoptosis in HCC (Table 4). Among the effects of metformin on cancer cell proliferation, activation of AMPK in the liver, muscle, and adipocytes has been shown to inhibit HCC proliferation by suppressing the upregulation of IGF-2 molecules and IGF-1 receptors.<sup>143</sup> In one in vitro and in vivo study with HCC cell lines, metformin was shown to reduce HCC growth

**Table 4** Experimental Studies on the Antitumor Effects of Metformin Against Hepatocellular Carcinoma (HCC)

Studies on Metformin			
Authors (Year)	Model	Drugs	Results
Miyoshi et al <sup>147</sup> (2014)	HCC cell lines Xenograft mice	Metformin	Metformin inhibited HCC growth and induced G1 cell cycle arrest.
Sun et al <sup>146</sup> (2016)	HCC cell lines	Metformin	Metformin induced apoptosis by activating miR-23a, a functional target of FOXA1.
Bhat et al <sup>145</sup> (2017)	Genetic HCC mouse models	Metformin	Metformin induced apoptosis by decreasing MCL-1 and 4E-BP levels.
Vacante et al <sup>143</sup> (2019)	HCC cell lines	Metformin	Metformin promoted AMPK activity and counteracted the overexpression of IGF-2 molecule and the IGF-1 receptor.
Sun et al <sup>144</sup> (2020)	HCC cell linesXenograft mice	Metformin alone or in combination with iron	Metformin promoted antitumor effects by inducing apoptosis and autophagy through PI3K/Akt/mTOR.

**Abbreviations:** MCL-1, myeloid cell leukemia 1; IGF-1, insulin-like growth factor 1; PI3K, phosphatidylinositol 3 kinases; mTOR, mammalian target of rapamycin.

and invasion through PI3K/AKT/mTOR pathway and to promote antitumor effects by inducing apoptosis and autophagy.<sup>144</sup> A genetic HCC mouse model experiment of effects on apoptotic pathways showed that metformin reduced tumor size and induced apoptosis by decreasing myeloid cell leukemia 1 (MCL-1) and phosphorylated eukaryotic initiation factor 4E and (eIF4E)-binding protein 1 (4E-BP1) levels.<sup>145</sup> In another in vitro study using HCC cell lines, metformin induced apoptosis by upregulating AMPK phosphorylation and p53 expression and activating miR-23a, a functional target of forkhead box protein A1 (FOXA1). The inhibition of p53 suppressed miR-23a upregulation by metformin, indicating that the AMPK/p53 signaling is involved in the induction of miR-23a.<sup>146</sup> We have also shown in previous in vitro and in vivo studies that metformin inhibits HCC growth and induces G1 cell cycle arrest via microRNA changes.<sup>147,148</sup> In addition, recent studies using multiple mouse models of NASH have shown that NASH causes changes in the inflammatory phenotype of hepatic CD8+ T cells, blunting the efficacy of PD-1 therapy; however, metformin treatment restores the efficacy of anti-PD-1 therapy against NASH-induced liver cancer.<sup>149</sup> Thus, investigating the interaction between the immune checkpoint inhibitor and metformin will contribute to improvement in the prognosis of patients with advanced HCC-related T2D and NASH, which is expected to increase in the future.

A basic study on the antitumor effects of DPP-4 inhibitors on HCC showed that anagliptin and vildagliptin did not affect the proliferation of Huh-7 and Li-7 cell lines in vitro and had no effect on cell cycle-related proteins such as p21, p27kip1, cyclin-dependent kinase 2 (CDK2), and retinoblastoma protein (Rb).<sup>150</sup> However, both anagliptin and vildagliptin inhibited xenograft HCC growth by natural killer and T-cell tumor accumulation in vivo. Furthermore, sitagliptin has improved the efficiency and duration of tumor-specific T-cell responses when used in combination with anti-programmed cell death 1 (PD1) blockade immunotherapy and other therapies. In an in vivo study using a tumor transplant mouse model, sitagliptin or anti-PD1 antibody monotherapy was shown to delay HCC growth. Interestingly, complete tumor regression was observed with sitagliptin plus anti-PD1 administration.<sup>151</sup> Tumor from sitagliptin-treated mice showed a remarkable change in the number of CD8+ T cells, promoting the transport of CD8+ T lymphocytes into the tumor. The study also indicated higher CD8+ T-cell infiltration in HCC tissue from patients treated with sitagliptin compared to that in patients not treated with it, suggesting that sitagliptin may improve the efficacy of PD1 blockade immunotherapy.

Among SGLT2 inhibitors, there has been some evidence regarding the antitumor effect of canagliflozin on HCC. In a report regarding the cytotoxic and antitumor effects of canagliflozin in combination with doxorubicin, canagliflozin significantly increased the cytotoxicity of doxorubicin in HepG2 cell line and enhanced the cellular uptake of doxorubicin by lowering the P-glycoprotein level.<sup>152</sup> In vivo analysis using the xenograft mouse model also showed that canagliflozin significantly increased the antitumor effects of doxorubicin. The same authors also elucidated the effects of canagliflozin on HCC development under hypoxia and showed that canagliflozin significantly inhibited hypoxia-induced metastasis, angiogenesis, and metabolic reprogramming in HCC cell lines by targeting the Akt/mammalian target of

rapamycin (mTOR) pathway and inhibiting the accumulation of hypoxia-inducible factor 1- $\alpha$  (HIF-1 $\alpha$ ) protein.<sup>153</sup> Another basic study showed that canagliflozin inhibited cell proliferation in HepG2 cell lines and that incubation with canagliflozin followed by exposure to  $\gamma$ -radiation more potently inhibited cell growth and clonogenic survival by disabling signaling pathways that contribute to metabolic reprogramming and tumor progression, leading to radio resistance and treatment failure.<sup>154</sup>

## Dyslipidemia and Liver Disease

Excess fat in the body is stored in hepatocytes in the form of lipid droplets covered with several structural proteins, which progress to chronic liver disease.<sup>155,156</sup> NAFLD develops from abnormalities in lipid metabolism, including systemic lipolysis, increased liver free fatty acid (FFA) uptake and very low-density lipoprotein synthesis, and decreased FFA oxidation and triglyceride (TG) export.<sup>157,158</sup> These alterations in lipid metabolism are associated with oxidative stress and liver inflammation in NAFLD patients, as well as the abnormal production of adipokines including resistin, visfatin, adiponectin, leptin, and retinol binding protein 4 (RBP4).<sup>159,160</sup>

Different lipid profiles, including TG and total cholesterol (TC) including low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) appear to have different risks of HCC development in patients with dyslipidemia. In the general population, low TC levels are strongly associated with a high risk of HCC development;<sup>161–165</sup> for every 39 mg/Dl increase in TC, about 50% reduction in HCC occurrence was observed.<sup>163</sup> Only a few studies have examined the association between other lipids and HCC, but low levels of TG and LDL-C are generally associated with a high risk of HCC occurrence, while the association with HDL-C levels was unknown.<sup>161,162</sup> Furthermore, in patients with chronic liver disease, as in the general population, TC levels have been shown to be inversely associated with the risk of HCC occurrence, although relatively few reports have shown the association between other lipid profiles and HCC occurrence. In patients with viral hepatitis (including HBV and HCV), NAFLD, and cirrhosis, higher TC levels were associated with a decreased risk of HCC occurrence.<sup>162,166–169</sup> The presence of chronic liver disease is associated with altered lipid metabolism, and serum TC levels in HCC patients were lower than healthy controls,<sup>170–173</sup> while lower TC levels were associated with severity of liver disease.<sup>163</sup>

## Suppression of HCC Occurrence of Dyslipidemia Drugs

Statins are one of the most important lipid-lowering agents, acting by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA), the rate-limiting enzyme in cholesterol biosynthesis. Statins not only significantly reduce the risk of cardiovascular morbidity and mortality, but have recently been shown to be effective against NASH and have even been associated with reduced mortality from cancer.<sup>174</sup> Several studies have reported that statin use decreased the risk of HCC development in patients with viral hepatitis and NAFLD.<sup>166–168,175–181</sup> A recent meta-analysis reported that statin use in patients with chronic liver disease reduced the risk of HCC occurrence with a hazard ratio of 0.57.<sup>181</sup> However, observational studies in the general population found no benefit of statin in preventing HCC occurrence,<sup>163,182</sup> nor did an RCT of the statin use for the presentation of cardiovascular disease.<sup>183,184</sup> Hypocholesterolemia in the natural course without statin use may be a potential risk factor for HCC development.<sup>161–165</sup> Since lower cholesterol would result in less frequent statin use, caution should be exercised in assessing the beneficial effects of statins against HCC.

## Antitumor Effects and Mechanism of Dyslipidemia Drugs on HCC

Although the mechanisms by which statins exert their antitumor effects on HCC are not yet fully elucidated, several reports have provided evidence for interrelated molecular pathways (Table 5). Statins inhibit cholesterol biogenesis by suppressing the conversion of HMG-CoA to mevalonic acid (MVA), as well as the production of derivatives of the MVA pathway, which has important effects on cell growth differentiation, membrane integrity, motility, signal transduction and other growth signals. Thus, statin administration produces antiproliferative, apoptosis-promoting, and anti-angiogenic effects.<sup>185,186</sup>

Certain statins generally inhibit cancer cell growth through inhibition of HMG-CoA reductase, followed by reduction of isoprenoid. Cerivastatin had been shown to inhibit Ras- and Rho-mediated cell proliferation,<sup>187</sup> while lovastatin-inhibited activation of the proteasome pathway and stabilizes p21 and p27.<sup>188</sup> In the liver, simvastatin and lovastatin have also been shown to inhibit hepatic astrocyte proliferation and their collagen steady-state levels.<sup>189</sup> An in vivo study

**Table 5** Experimental Studies on the Antitumor Effects of Statins Against Hepatocellular Carcinoma (HCC)

Studies on Statins			
Authors (Year)	Model	Drugs	Results
Tatusta et al <sup>190</sup> (1998)	N-nitrosomorpholine-induced HCC rats	Pravastatin	Pravastatin suppressed hepatocarcinogenesis by inhibiting of cell proliferation and inducing of apoptosis
Relja et al <sup>195</sup> (2011)	HCC cell lines	Simvastatin	Simvastatin inhibited angiogenesis and cell adhesion by decreasing of integrin expression and Rho-dependent kinase.
Spampanato et al <sup>191</sup> (2012)	HCC cell lines	Simvastatin	Simvastatin induced apoptosis by activating Bax and downregulating Bcl-2 expression.
Kah et al <sup>192</sup> (2012)	HCC cell lines	Fluvastatin, simvastatin, and lovastatin	Statins induced HCC cells apoptosis. Antitumor effects of statins was reduced by p53 overexpression
Zhou et al <sup>198</sup> (2016)	HCC cell lines Xenograft mice	Atorvastatin	Atorvastatin improved hypotoxic resistance to sorafenib in HCC by inactivation of hypoxia-induced YAP.
Ridruejo et al <sup>196</sup> (2018)	DEN- and HCB-induced HCC rats	Atorvastatin and simvastatin	Statins inhibited HCC growth by regulating TGF- $\beta$ and thyroid hormones
Feng et al <sup>197</sup> (2020)	HCC cell lines	Simvastatin	Simvastatin decreased proliferation and increased apoptosis by inhibited HIF-1 $\alpha$ /PPAR- $\gamma$ /PKM2 axis.

**Abbreviations:** YAP, yes-associated protein; TGF, transforming growth factor; HIF-1 $\alpha$ , hypoxia-inducible factor 1 $\alpha$ ; PPAR- $\gamma$ , peroxisome proliferator-activated receptor  $\gamma$ ; PKM2, pyruvate kinase M2 isoform.

showed that pravastatin inhibited p21ras isoprenylation in a rat model of N-nitrosomorpholine-induced hepatocarcinogenesis and the development of neoplastic liver nodule formation by inhibiting cell proliferation and inducing apoptosis.<sup>190</sup> Conversely, lovastatin induced cell cycle arrest by inhibiting G1/S and G2/M transitions. Furthermore, induction of apoptosis is an important mechanism of tumor suppression of statins; simvastatin has been shown to induce Bax expression and inhibit Bcl-2 expression in several cancer cell lines including HCC,<sup>191</sup> thereby promoting DNA fragmentation. Interestingly, statin-mediated apoptosis was observed only in cancer cells, while non-cancerous fibroblasts showed no signs of apoptosis. Another report showed that the antitumor effect of statins was associated with the overexpression of p53. For instance, the HuH-7 cell line, which overexpresses p53, was sensitized to statin-induced apoptosis by stable knockdown of endogenous p53.<sup>192</sup> In addition to inhibiting cell proliferation and inducing apoptosis, angiogenesis was an important mechanism of antitumor effects. Several studies in various cancer types have shown that statins inhibit cell migration and proliferation.<sup>193,194</sup> In HCC, simvastatin decreases tumor cell proliferation in a dose-dependent manner, impairs tumor cell adhesion to the endothelial cell monolayer, and decreases tumor cell invasion.<sup>195</sup> However, there are few reports of statins inhibiting angiogenesis in HCC.

A recent study involving two in vivo rat models of HCC induced with DEN and hexachlorobenzene (HCB) reported that atorvastatin and simvastatin inhibit HCC growth by regulating TGF- $\beta$ 1 and thyroid hormones.<sup>196</sup> There are also increasing number of reports that statins improve sorafenib resistance in HCC, and simvastatin inhibited the HIF-1 $\alpha$ /peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ )/pyruvate kinase 2 axis, resulting in decreased proliferation and increased apoptosis in HCC cells, which can re-sensitize HCC cells to sorafenib.<sup>197</sup> According to another report, inactivation of hypoxia-induced Yes associate-protein by statins improved hypoxic resistance to sorafenib in HCC cells.<sup>198</sup>

Regarding dyslipidemia drugs other than statins, such as bezafibrate, these can potentiate the antitumor effects of PD-1 antibodies against other cancer types, including colorectal cancer, and regulate PPAR- $\gamma$  coactivator 1 $\alpha$ , a molecule that exhibits mitochondrial activity.<sup>199</sup> However, there is virtually no evidence of antitumor effects against HCC, and further basic studies are needed.

## Conclusion

Metabolic syndrome, including hypertension, T2D, dyslipidemia, and obesity, is associated with the development of HCC. In addition, these diseases can develop as adverse events during systemic therapy for advanced HCC. Interestingly,

some metabolic syndrome medications show antitumor effects against HCC, while others do not. Our current review provides valuable evidence on the metabolic syndrome medications that may have an inhibitory effect on the development and progression of HCC in patients with chronic liver disease, including steatohepatitis, that may develop metabolic syndrome as a comorbidity. Various mechanisms have been reported for the antitumor effects of metabolic syndrome medications, not all of which have been elucidated in basic studies. Analysis of these mechanisms is beneficial for HCC patients with metabolic syndrome, and metabolic syndrome medications may contribute to potential therapeutic strategies.

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