

REVIEW ARTICLE

Alpha lipoic acid as a modulator of the AMPK-p53 axis: Mechanisms and therapeutic potential in hepatocellular carcinoma progression

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Abstract

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, with metastasis significantly impacting patient outcomes. Alpha lipoic acid (ALA), a potent antioxidant, has shown promise in cancer treatment due to its ability to modulate key cellular pathways. The AMP-activated protein kinase (AMPK)-p53 axis plays a critical role in regulating cellular metabolism and tumor suppression, making it an attractive target for HCC therapy. This review aims to elucidate the potential of ALA as a modulator of the AMPK-p53 axis in HCC progression, focusing on its mechanisms and therapeutic potential in inhibiting metastasis. ALA exerts its anti-cancer effects through multiple mechanisms, including direct antioxidant activity, activation of AMPK, and modulation of p53 function. In HCC, ALA has been shown to inhibit cell proliferation, induce apoptosis, and suppress epithelial-mesenchymal transition, a key process in metastasis. ALA activates AMPK, which in turn inhibits mammalian target of rapamycin signaling and promotes p53 activation. This leads to cell cycle arrest, increased apoptosis, and reduced metastatic potential. In addition, ALA's ability to modulate mitochondrial function and reduce oxidative stress further contributes to its anti-cancer properties. Preclinical studies have demonstrated ALA's efficacy in reducing tumor growth and metastasis in HCC models, suggesting its potential as an adjunct therapy. The modulation of the AMPK-p53 axis by ALA represents a promising approach for HCC treatment, particularly in addressing metastasis. Further research is needed to optimize ALA's therapeutic potential and evaluate its efficacy in combination with existing HCC therapies. This review highlights the importance of targeting metabolic and tumor suppressor pathways in developing novel strategies for HCC management.

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1. Background

1.1. Overview of hepatocellular carcinoma (HCC)

HCC is the most common primary malignancy of the liver, accounting for approximately 75% of all liver cancer cases. Globally, it ranks as the sixth most common cancer and the third leading cause of cancer-related mortality.¹⁻⁴ The incidence of HCC varies across regions, with the highest rates observed in East Asia and sub-Saharan Africa, primarily due to high rates of Hepatitis B virus (HBV) infection.^{5,6} In Western countries, the incidence is increasing due to the rising prevalence of Hepatitis C virus (HCV) infection, alcohol-related liver disease, and metabolic dysfunction-associated steatotic liver disease (MASLD), which are significant risk factors for HCC development.⁷ HCV infection epidemiology presents a complex picture, with overall prevalence declining in many regions due to improved screening, treatment, and prevention efforts. However, this trend is not uniform across all populations. Some groups, particularly younger adults and people who inject drugs, are experiencing rising incidence rates. This dichotomy reflects the success of public health interventions in reducing HCV prevalence in the general population while highlighting persistent challenges in high-risk groups. Factors contributing to increased incidence in certain populations include the opioid epidemic, inadequate harm reduction services, and gaps in healthcare access. Understanding these nuanced trends is crucial for developing targeted strategies to further reduce HCV transmission and improve outcomes across all affected populations.⁸⁻¹¹

Diabetes, obesity, and MASLD are interconnected risk factors for HCC. Obesity often leads to insulin resistance and Type 2 diabetes, both of which contribute to liver fat accumulation and inflammation characteristic of MASLD. This chronic liver condition can progress to fibrosis, cirrhosis, and ultimately HCC. The metabolic dysregulation associated with these conditions promotes hepatocellular injury, oxidative stress, and altered cell signaling, creating an environment conducive to cancer development. Understanding this relationship is crucial for developing comprehensive prevention and management strategies for HCC.^{12,13} HCC predominantly arises in the setting of chronic liver disease and cirrhosis, with more than 80% of cases occurring in cirrhotic patients.^{5,14,15} Chronic HBV and HCV infections remain the most common etiological factors, although alcohol abuse and metabolic disorders such as MASLD are increasingly contributing to the global burden of HCC. Other risk factors include aflatoxin exposure, diabetes, and obesity.¹⁶⁻¹⁸ MicroRNAs (miRNAs) regulate gene expression in HCC by binding to target mRNAs, inhibiting translation or

inducing degradation. They can act as oncogenes or tumor suppressors, influencing cell proliferation, apoptosis, and metastasis. Dysregulation of specific miRNAs contributes to HCC progression by altering key signaling pathways and promoting tumor growth, invasion, and drug resistance.¹⁹ The current standard of care for HCC depends on factors such as tumor stage, liver function, and overall patient health. Early-stage HCC may be treated with resection,^{20,21} liver transplantation, or ablation.

However, many patients present with advanced disease, for which systemic therapies such as tyrosine kinase inhibitors (*e.g.*, sorafenib and lenvatinib) and immune checkpoint inhibitors (*e.g.*, nivolumab) are used. Despite these therapeutic options, the prognosis remains poor due to late diagnosis, resistance to treatment, and high rates of recurrence and metastasis.²²⁻²⁴ The incidence of HCC varies significantly across geographic regions due to several influencing factors. East Asia and sub-Saharan Africa have the highest rates, primarily due to the high prevalence of HBV infection in these areas. In contrast, Western countries are experiencing an increasing incidence of HCC, largely attributed to rising rates of HCV infection, alcohol-related liver disease, and MASLD. The variation in HCC incidence is also influenced by differences in screening practices, access to healthcare, and implementation of vaccination programs (particularly for HBV). Projections for HCC incidence suggest a continued rise globally, driven by aging populations and increasing prevalence of non-alcoholic fatty liver disease (NAFLD). As populations age, the cumulative risk of chronic liver diseases grows. Simultaneously, rising obesity rates contribute to NAFLD, a significant risk factor for HCC. These trends indicate a likely surge in HCC cases worldwide in coming decades. Environmental factors, such as aflatoxin exposure in certain regions, further contribute to the geographic disparities in HCC incidence. In addition, the aging population in many developed countries is leading to an increased prevalence of chronic liver diseases, which are major risk factors for HCC development. These regional differences highlight the complex interplay of viral, environmental, and lifestyle factors in HCC epidemiology and underscore the need for tailored prevention and screening strategies across different populations.²⁵⁻²⁹

1.2. Relevance of targeting migration and invasion in HCC

Metastasis is a critical factor in HCC prognosis as it significantly contributes to disease progression and poor survival outcomes. The liver's unique blood supply and structural environment make it particularly vulnerable to metastatic spread. Tumor invasion and migration in HCC are driven by complex interactions between

cancer cells and their microenvironment, involving various signaling pathways that regulate cytoskeletal reorganization, cell adhesion, and matrix degradation.^{30,31} HCC patients can be categorized into subgroups based on distinct clinical and molecular characteristics. These include early-stage versus advanced-stage tumors, viral hepatitis-associated versus non-viral HCC, and tumors with specific genetic mutations (e.g., *TP53*, *CTNNB1*). Other subgroups are defined by metabolic risk factors, cirrhosis status, and tumor microenvironment features, influencing prognosis and treatment response. Metastatic HCC profoundly impairs patients' quality of life through multiple interconnected mechanisms. As the cancer spreads beyond the liver, it can cause severe pain, fatigue, and weakness, significantly limiting patients' daily activities and independence. Metastases to organs like the lungs or bones may lead to breathing difficulties, fractures, or neurological symptoms, further compromising mobility and comfort. The progression of liver dysfunction often results in complications such as ascites, jaundice, and hepatic encephalopathy, which can cause physical discomfort, altered mental status, and social embarrassment. Patients frequently experience appetite loss, weight loss, and malnutrition, contributing to overall debilitation. The psychological burden of advanced cancer, including anxiety, depression, and fear of death, can be overwhelming. In addition, the side effects of treatments like chemotherapy or radiation may further diminish the quality of life. Social and financial strains often accompany the disease, as patients may be unable to work and face mounting medical expenses. The cumulative impact of these factors can lead to social isolation, loss of self-esteem, and a diminished sense of personal autonomy, severely affecting the overall well-being and life satisfaction of patients with metastatic HCC.³² Targeting the molecular mechanisms underlying migration and invasion is crucial for improving HCC outcomes. Metastasis not only complicates treatment but also limits the efficacy of local therapies. Thus, understanding the biological processes that contribute to HCC metastasis, including epithelial-mesenchymal transition (EMT), is essential for developing novel therapeutic strategies aimed at halting disease progression.³³⁻³⁷

1.3. Alpha lipoic acid (ALA)

ALA is a naturally occurring compound with a well-established role as a potent antioxidant. Structurally, ALA is a disulfide derivative of octanoic acid with both hydrophilic and hydrophobic properties, allowing it to function in various cellular environments. ALA is synthesized endogenously and can also be obtained through dietary sources such as red meat and green vegetables.³⁸⁻⁴⁰

In cell culture experiments, ALA concentrations often range from 0.1 to 2 mM, with treatment durations typically between 24 and 72 h. In animal studies, oral ALA doses commonly range from 10 to 100 mg/kg body weight/day, with treatment durations varying from a few weeks to several months, depending on the specific research question and model used.⁴¹⁻⁴³ Pharmacologically, ALA exhibits a broad range of biological activities, including free radical scavenging, metal chelation, and modulation of mitochondrial function. It is widely used as a neuroprotective agent, particularly in the treatment of diabetic neuropathy. More recently, ALA has garnered attention for its potential anti-cancer properties, with emerging evidence suggesting its ability to inhibit cancer cell proliferation, invasion, and metastasis. In the context of liver cancer, ALA's antioxidant and anti-inflammatory effects may offer protection benefits, making it a promising candidate for therapeutic intervention in HCC.^{44,45}

2. Mechanisms of tumor progression in HCC

2.1. Hallmarks of HCC metastasis

HCC metastasis is a complex, multi-step process involving several molecular and cellular changes. One of the key mechanisms driving HCC progression is EMT, a phenotypic transformation in which epithelial cells acquire mesenchymal characteristics, leading to enhanced motility, invasion, and resistance to apoptosis.^{46,47} In HCC research, several common metastasis markers are often evaluated alongside EMT markers to provide a comprehensive assessment of metastatic potential. These include matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, which play crucial roles in extracellular matrix degradation and tumor invasion. Vascular endothelial growth factor is another important marker, as it promotes angiogenesis and vascular permeability, facilitating tumor growth and metastasis. Integrins, cell adhesion molecules that mediate interactions between cells and the extracellular matrix, are also frequently studied. In addition, CD44, a cell-surface glycoprotein involved in cell-cell interactions, cell adhesion, and migration, and osteopontin, a protein that plays a role in cell attachment and signaling, are often assessed in metastasis studies to gain a more complete understanding of the metastatic process in HCC.⁴⁸⁻⁵²

During EMT, cancer cells downregulate epithelial markers such as E-cadherin and upregulate mesenchymal markers such as N-cadherin and vimentin, allowing them to detach from the primary tumor and invade surrounding tissues.⁵³⁻⁵⁵ Several signaling pathways are implicated in HCC metastasis, including the Wnt/ β -catenin, transforming growth factor-beta (TGF- β), and mitogen-activated protein kinase (MAPK) pathways.

These pathways regulate key processes such as cytoskeleton remodeling, cell adhesion, and extracellular matrix degradation, all of which are critical for tumor invasion and migration. Dysregulation of these pathways contributes to the aggressive nature of HCC and its propensity for early metastasis.⁵⁶⁻⁶¹

2.2. Key pathways targeted by therapeutic agents

Therapies targeting the molecular drivers of HCC metastasis are under active investigation, as depicted in Table 1. The Wnt/ β -catenin pathway, for example, is frequently dysregulated in HCC and plays a crucial role in EMT and cell migration. Inhibitors targeting this pathway have demonstrated efficacy in preclinical models, but clinical translation remains challenging. The TGF- β pathway is another critical target, as it promotes EMT and immune evasion. Small-molecule inhibitors of TGF- β signaling are being explored for their potential to suppress HCC metastasis.⁶²⁻⁶⁸ In addition, the MAPK pathway, particularly the extracellular signal-regulated kinase (ERK) cascade, is involved in promoting HCC cell proliferation and invasion. Inhibitors of this pathway, such as sorafenib, have been approved for advanced HCC, though their impact on metastasis is limited. Novel agents that can more effectively target these pathways are needed to improve outcomes for patients with metastatic HCC.⁶⁹

3. Molecular mechanisms behind the suppressive roles of ALA against cancer

3.1. Antioxidant properties of ALA

As a potent antioxidant, ALA plays a critical role in neutralizing free radicals and reducing oxidative stress, acting a key contributor to cancer development and progression. ALA can directly scavenge reactive oxygen

species (ROS) and regenerate other antioxidants such as glutathione and Vitamin C. In addition, ALA exerts its antioxidant effects by modulating the activity of transcription factors like nuclear factor erythroid 2-related factor 2 (Nrf2), which regulates the expression of antioxidant response genes.⁷⁰⁻⁷² Autophagy, a cellular recycling process, plays a crucial role in linking ALA, AMP-activated protein kinase (AMPK) activation, and cancer cell inhibition. ALA activates AMPK, which in turn stimulates autophagy through mammalian target of rapamycin (mTOR) inhibition and Unc-51 like Autophagy Activating Kinase 1 (ULK1) activation. This enhanced autophagy can lead to the degradation of damaged cellular components and oncogenic proteins, potentially suppressing cancer cell growth and survival. In addition, autophagy modulation by the ALA-AMPK axis may sensitize cancer cells to metabolic stress and chemotherapy. However, the complex nature of autophagy in cancer necessitates further research to fully elucidate its role in ALA-mediated cancer cell inhibition.⁷³⁻⁷⁵

ALA potentially influences HCC biology through several key mechanisms: it acts as a potent antioxidant, reducing oxidative stress and inflammation that contribute to liver damage and cancer progression. ALA activates the AMPK-p53 signaling axis, which inhibits cancer cell proliferation, induces apoptosis, and suppresses metastasis by downregulating EMT markers. It modulates mitochondrial function, potentially disrupting cancer cell metabolism. ALA also shows anti-angiogenic properties and may enhance the efficacy of existing HCC therapies when used in combination.⁷⁶

3.2. Potential role of ALA in cancer

There is accumulating evidence from preclinical and clinical studies suggesting that ALA has anti-cancer

Table 1. Key molecular pathways in hepatocellular carcinoma progression and metastasis

Pathway	Key components	Role in HCC progression	Relevance to metastasis	References
Wnt/ β -catenin pathway	Wnt ligands, β -catenin, GSK-3 β	Promotes EMT, cell proliferation, and resistance to apoptosis	Enhances cell migration and invasion	46-51
MAPK pathway	ERK, JNK, p38 MAPK	Regulates cell proliferation and differentiation	Increases tumor cell invasion and metastasis	52-58
TGF- β pathway	TGF- β , SMAD proteins	Induces EMT, immune evasion, and fibrosis	Strengthens metastatic potential	59
mTOR pathway	mTOR, Raptor, Rictor	Promotes cell growth, protein synthesis, and survival	Supports proliferation and metastatic spread	52-58
AMPK pathway	AMPK, LKB1, ACC	Inhibits anabolic pathways, promotes apoptosis under stress	Suppresses migration and invasion	70

Abbreviations: ACC: Acetyl-CoA Carboxylase; AMPK: AMP-activated protein kinase; EMT: Epithelial-mesenchymal transition; ERK: Extracellular Signal-Regulated Kinase; GSK-3 β : Glycogen Synthase Kinase 3 Beta; HCC: Hepatocellular carcinoma; JNK: c-Jun N-terminal Kinase; LKB1: Liver Kinase B1; MAPK: Mitogen-Activated Protein Kinase; mTOR: Mammalian target of rapamycin; TGF- β : Transforming growth factor beta; Wnt: Wingless/Integrated.

properties, as presented in Figure 1. Several studies have demonstrated that ALA can inhibit the proliferation of various cancer cell types, including breast, colon, and liver cancer cells. In HCC models, ALA has been shown to reduce cell viability and induce apoptosis through its effects on mitochondrial function and oxidative stress pathways. ALA's anti-metastatic potential is particularly relevant to HCC, given the role of oxidative stress in promoting EMT and cell migration. Experimental studies have demonstrated that ALA can inhibit key markers of EMT, such as vimentin and N-cadherin while upregulating epithelial markers like E-cadherin. These findings suggest that ALA may suppress the metastatic spread of HCC by reversing EMT and inhibiting cancer cell migration.⁷⁷

3.3. ALA in liver disease

ALA has long been recognized for its protection effects, particularly in the context of chronic liver diseases such as cirrhosis, MASLD, and viral hepatitis. For studying ALA effects in HCC, a commonly used animal model is the diethylnitrosamine (DEN)-induced HCC model in rats or mice. For cell lines, HepG2 or Huh7 human HCC cell lines are frequently used *in vitro*. These models allow researchers to investigate ALA's effects on HCC development, progression, and metastasis. In animal models of liver injury, ALA has been shown to reduce oxidative stress, inflammation, and fibrosis. These effects are mediated through ALA's ability to restore mitochondrial function, reduce ROS production, and modulate inflammatory signaling pathways.⁷⁸ In the context of HCC, ALA's protection properties may help mitigate the progression of liver disease and reduce the risk of tumor development. Moreover, ALA's ability to modulate key pathways involved

in cell proliferation and migration makes it a promising candidate for combination therapies aimed at both preventing liver disease progression and inhibiting HCC metastasis.⁷⁹

4. AMPK-p53 axis as the therapeutic target for HCC

4.1. AMPK: Metabolic regulator and tumor suppressor

As the master regulator of cellular energy homeostasis that plays a vital role in maintaining metabolic balance, AMPK is activated in response to cellular stress, such as low energy levels, and functions to restore energy balance by promoting catabolic processes such as fatty acid oxidation and inhibiting anabolic processes like protein synthesis. Beyond its metabolic functions, AMPK acts as a tumor suppressor by inhibiting cell growth and proliferation, particularly under conditions of nutrient deprivation or hypoxia. In cancer, AMPK activation has been shown to suppress tumor progression by inhibiting key signaling pathways involved in cell proliferation and survival, such as the mTOR pathway. Moreover, AMPK can inhibit cancer cell migration and invasion by modulating the cytoskeleton and cell adhesion molecules.⁸⁰

4.2. p53: The guardian of the genome

The tumor suppressor protein p53 is known as the “guardian of the genome” due to its critical role in maintaining genomic stability and preventing tumor formation. p53 regulates a wide array of cellular processes, including apoptosis, cell cycle arrest, and DNA repair. In the context of cancer, p53 is often mutated or inactivated, leading to uncontrolled cell growth and resistance to apoptosis. In addition to its role in tumor suppression, p53 has been shown to inhibit metastasis by regulating genes involved in cell adhesion, migration, and invasion. p53 can suppress EMT and maintain epithelial characteristics in cancer cells, thereby reducing their migratory and invasive potential.^{81,82}

4.3. Crosstalk between AMPK and p53 in HCC

There is growing evidence that AMPK and p53 function in a coordinated manner to suppress tumor progression. AMPK can activate p53 in response to metabolic stress, leading to cell cycle arrest and apoptosis. This crosstalk between AMPK and p53 is particularly relevant in HCC, where metabolic reprogramming and resistance to apoptosis are common features of tumor progression. In HCC, activation of the AMPK-p53 axis has been shown to inhibit cell migration and invasion by downregulating key markers of EMT and suppressing pro-metastatic signaling pathways like mTOR. The interplay between

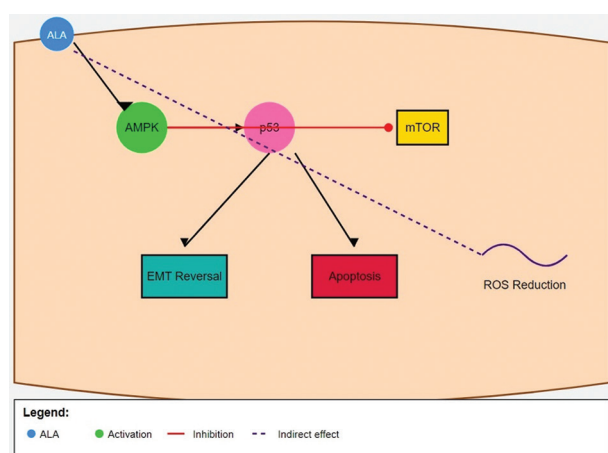


Figure 1. Molecular mechanisms behind the role of alpha lipoic acid in suppressing cancer

Abbreviations: ALA: Alpha lipoic acid; AMPK: AMP-activated protein kinase; EMT: Epithelial-mesenchymal transition; mTOR: Mammalian target of rapamycin; ROS: Reactive oxygen species.

AMPK, p53, and other signaling pathways involved in HCC metastasis, such as the MAPK and Wnt/ β -catenin pathways, highlights the potential of targeting this axis for therapeutic intervention.⁸³

Fasting has emerged as a potential strategy to impact AMPK activation and HCC progression. During fasting, cellular energy depletion activates AMPK, which promotes catabolic processes and inhibits anabolic pathways. This metabolic shift can suppress HCC cell proliferation and induce apoptosis. AMPK activation also enhances autophagy, potentially eliminating damaged cellular components and oncogenic proteins. Furthermore, fasting-induced AMPK activation may sensitize HCC cells to chemotherapy and reduce systemic inflammation.⁸⁴⁻⁸⁶

5. ALA and the AMPK-p53 axis in HCC

5.1. Preclinical studies of ALA on HCC cells

Recent preclinical studies have demonstrated that ALA can inhibit HCC cell migration and invasion by activating the AMPK-p53 axis, as illustrated in Figure 2. In HCC cell lines, ALA treatment has been shown to reduce cell viability in a dose-dependent manner, while also inhibiting key markers of EMT, such as vimentin and N-cadherin. These effects are associated with the activation of AMPK and the subsequent activation of p53, leading to the suppression of pro-metastatic signaling pathways. Mechanistic studies have further revealed that ALA can induce apoptosis in HCC cells by promoting mitochondrial dysfunction and oxidative stress, both of which are regulated by the AMPK-p53 axis. The ability of ALA to modulate these pathways suggests that it may be effective in inhibiting not only HCC proliferation but also its metastatic spread.⁸⁷

5.2. ALA-induced activation of AMPK-p53 axis

ALA's activation of the AMPK-p53 axis in HCC cells is a key mechanism underlying its anti-metastatic effects. By activating AMPK, ALA can inhibit mTOR signaling, which is known to promote cell growth and survival in HCC. In addition, ALA-induced activation of p53 leads to the upregulation of pro-apoptotic genes and the downregulation of genes involved in EMT and metastasis. This dual regulation of AMPK and p53 positions ALA as a promising therapeutic agent for targeting both the metabolic and proliferative aspects of HCC progression.⁸⁸

AMPK plays a pivotal role in regulating metabolism through hormonal pathways. It influences the production and sensitivity of key metabolic hormones such as insulin, leptin, and adiponectin. AMPK activation enhances insulin sensitivity, improving glucose uptake and utilization. It also modulates leptin signaling, affecting appetite regulation and energy expenditure. AMPK interacts with adiponectin, promoting fatty acid oxidation and glucose uptake. Furthermore, AMPK influences the secretion of hormones from the hypothalamus, thyroid, and adrenal glands, coordinating whole-body energy balance. This hormonal control allows AMPK to orchestrate metabolic responses across multiple tissues, maintaining energy homeostasis under various physiological conditions.^{81,89,90}

5.3. Comparison with other AMPK activators

In addition to activating AMPK and p53, ALA exerts effects on HCC through modulating ROS, inhibiting inflammation and angiogenesis, and inducing mitochondrial dysfunction and apoptosis. ALA suppresses EMT by downregulating proteins involved in migration

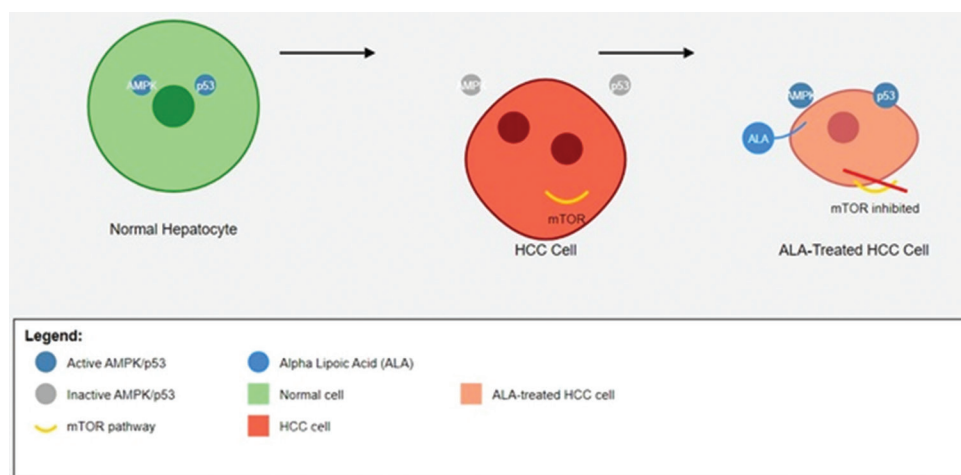


Figure 2. Modulation of AMPK-P53 Axis by Alpha lipoic Acid and in Hepatocellular Carcinoma

Abbreviations: ALA: Alpha lipoic acid; AMPK: AMP-activated protein kinase; HCC: Hepatocellular carcinoma; mTOR: Mammalian target of rapamycin; ROS: Reactive oxygen species.

and invasion like vimentin and upregulating epithelial markers. It also influences metabolic pathways involved in tumor proliferation and growth like mTOR inhibition, thus impacting multiple pathways crucial to HCC progression. ALA's ability to activate AMPK is comparable to other well-known AMPK activators, such as metformin and AICAR as depicted in Table 2. However, ALA offers certain advantages, including its antioxidant properties and ability to modulate mitochondrial function. While metformin has been shown to inhibit HCC proliferation, its effects on metastasis are less well-established. In contrast, ALA's dual role in inhibiting both proliferation and metastasis makes it a more attractive candidate for combination therapies in HCC.⁹¹

6. Therapeutic potential of ALA in HCC

6.1. Clinical relevance of targeting migration/invasion in HCC

Promising biomarkers for early HCC diagnosis and treatment monitoring include alpha-fetoprotein, proteins produced by tumor cells such as des-gamma-carboxy prothrombin and glypican-3, and imaging markers like ultrasound contrast agents, which allow for non-invasive detection of small tumors during routine screening. ALA activates the energy sensor AMPK, which phosphorylates and inhibits mTOR, a central driver of anabolic processes and cell growth.⁹² ALA appears to exert selective anti-tumor effects on HCC cells while largely sparing normal liver cells. Studies have shown that ALA reduces viability specifically in HCC cell lines through AMPK-p53 axis activation and ROS induction. In contrast, ALA displays low toxicity in normal hepatocyte cell models and animal

liver tissue.⁹³⁻⁹⁸ This selectivity may arise from ALA targeting dysregulated metabolic and signaling pathways upregulated in malignant transformation like mTOR and EMT proteins. Moreover, normal liver cells possess more robust antioxidant defenses than HCC cells against ALA's pro-oxidant activity.⁹⁹

HCC tumors are highly heterogeneous with diverse genetic and molecular profiles influencing pathogenesis and treatment response. ALA's mechanism of pleiotropic pathway modulation may not benefit all HCC subtypes equally, as some may harbor additional mutations shunting key regulatory nodes like AMPK or lack molecular traits ALA depends on. Identifying biomarkers predictive of ALA sensitivity through tumor profiling could help select patients most likely to benefit. Combination regimens may also help overcome acquired resistance by simultaneously targeting alternate compensatory routes.¹⁰⁰

Activated AMPK also phosphorylates tumor suppressor p53, enhancing its stability and transcriptional activity. p53 then promotes apoptosis through upregulation of pro-apoptotic proteins like Bcl-2-associated X protein (Bax) and represses EMT by inhibiting twist-related protein 1 (TWIST), snail family transcriptional repressor 1 (SNAIL) and other transcriptional factors. Together, ALA-induced AMPK-p53 activation downregulates mTOR and EMT pathways, restricting nutrient availability, and inducing cell cycle arrest and apoptosis while suppressing migration/invasion critical to HCC progression. ALA precisely targets these interconnected metabolic and proliferation regulators.^{101,102} Diet and nutritional status can impact ALA's efficacy by affecting its absorption, distribution, and metabolism. Adequate dietary ALA

Table 2. Effects of ALA on hepatocellular carcinoma cells

Effect	Mechanism	Outcome on HCC cells	Comparison with other AMPK activators	References
Reduction in cell viability	Induction of mitochondrial dysfunction and oxidative stress	Decreased cell growth and proliferation	Comparable with metformin and AICAR	91
Induction of apoptosis	Activation of p53, suppression of mTOR, upregulation of Bax	Increased apoptosis and reduced survival	Metformin primarily affects cell proliferation	91
Inhibition of migration	Suppression of EMT markers (vimentin, N-cadherin), upregulation of E-cadherin	Reduced migratory capacity and invasion potential	ALA has stronger anti-metastatic activity	106
Activation of AMPK	Direct activation of AMPK, leading to downstream effects on p53	Inhibition of mTOR, suppression of cell growth	Similar to metformin but with added antioxidant effects	106
Reduction in ROS	Scavenging of free radicals, modulation of mitochondrial function	Decreased oxidative stress, reducing damage to cellular components	ALA has superior antioxidant properties	107

Abbreviations: AICAR: 5-Aminoimidazole-4-carboxamide ribonucleotide; ALA: Alpha lipoic acid; AMPK: AMP-activated protein kinase; Bax: Bcl-2-associated X protein; EMT: Epithelial-mesenchymal transition; HCC: Hepatocellular carcinoma; mTOR: Mammalian target of rapamycin; ROS: Reactive oxygen species.

intake enhances endogenous levels, augmenting treatment effects. However, poor nutritional status in HCC patients reduces bioavailability and antioxidant protection. Macronutrients influence ALA pharmacokinetics through metabolic interactions. Nutraceuticals used in combination treatments like curcumin act synergistically to sensitize tumors through complementary mechanisms. Considering that nutritional covariates and supplementation holds value for optimizing ALA's clinical translation, investigations on standardized dietary guidance are warranted for harnessing the interaction between ALA and diet.^{103,104}

Targeting migration and invasion is critical for improving outcomes in HCC, particularly in patients with advanced or metastatic disease. Current therapies, such as tyrosine kinase inhibitors and immune checkpoint inhibitors, primarily target tumor growth and immune evasion but have limited efficacy in preventing metastasis. The ability of ALA to inhibit HCC cell migration and invasion through the activation of the AMPK-p53 axis makes it a promising candidate for combination therapies aimed at improving survival in HCC patients.¹⁰⁵

6.2. Combination therapies involving ALA

ALA shows promise in combination with HCC therapies. As an adjuvant to chemotherapy, ALA may improve outcome by reducing toxicity through its antioxidant effects and sensitizing tumors through AMPK activation. The anti-inflammatory and immunomodulatory properties of ALA support its combined use with immunotherapy to address resistance mechanisms. ALA could strengthen checkpoint inhibitors' efficacy by limiting immunosuppressive tumors and may also synergize with kinase inhibitors like sorafenib that target growth pathways, comprehensively hindering HCC.¹⁰⁶ It also has the potential to enhance the efficacy of existing HCC therapies when used in combination. For example, combining ALA with sorafenib, a multi-kinase inhibitor, may provide synergistic effects by simultaneously targeting multiple pathways involved in HCC progression. In addition, ALA may enhance the efficacy of immune checkpoint inhibitors by reducing the immunosuppressive effects of oxidative stress and inflammation in the tumor microenvironment.¹⁰⁷

6.3. Limitations and challenges in translating preclinical findings to clinical application

Tumor heterogeneity may engender resistance to ALA through mutations disrupting pathways crucial to its mechanism. In addition, cancer cells can evolve adaptive resistance by activating bypass signaling to circumvent AMPK and p53. Chronic ALA exposure could elicit feedback signaling reprogramming metabolism and limiting pro-apoptotic effects. Epigenetic changes may

epigenetically silence sensitizing factors. Combining ALA with agents blocking compensatory routes like MAPK may curb resistance. Sequential or intermittent dosing holds promise to thwart resistance by alternately engaging distinct programs.¹⁰⁸ Despite the promising preclinical data, several challenges remain in translating ALA's therapeutic potential to clinical application. One of the primary challenges is ALA's bioavailability and pharmacokinetics in humans, as oral administration of ALA has been shown to result in limited systemic exposure. Moreover, the optimal dosing and potential toxicity of ALA in cancer patients have not been well-established. Addressing these challenges through formulation improvements and clinical trials is essential for advancing ALA as a therapeutic option for HCC.¹⁰⁹

7. Future directions and perspectives

7.1. Emerging areas of research

Further research is needed to fully elucidate the mechanisms by which ALA modulates the AMPK-p53 axis in HCC, as depicted in [Table 3](#). Current first-line therapies for HCC target tumor growth and immune evasion with limited efficacy against metastasis. ALA represents an attractive candidate for combination regimens through its distinct mechanisms uniquely inhibiting proliferation and invasion. Future research should explore synergies of ALA with immunotherapy or kinase inhibitors to comprehensively apprehend HCC at multiple stages through ALA's multi-targeted approach modulating key pathways and microenvironmental influences beyond single agents.¹¹⁰ Understanding the molecular determinants of ALA's efficacy, such as specific biomarkers that predict response, will be critical for developing personalized treatment strategies. Moreover, additional studies are needed to explore the potential of ALA in combination with other targeted therapies, particularly those that inhibit key pathways involved in HCC migration and invasion.¹¹¹

7.2. Clinical trials and translational research

Some key challenges in conducting ALA clinical trials for HCC include variable oral bioavailability of ALA formulations between studies hindering result comparisons. Establishing optimal dosing regimens is critical, given the lack of human pharmacokinetic data. Trial quality demands standardized ALA preparations to minimize inconsistencies. Biomarkers must correlate ALA exposure with responses to confirm mechanisms of action. While preclinical studies have shown promising results, there is a need for well-designed clinical trials to evaluate the safety and efficacy of ALA in HCC patients. Such trials should incorporate biomarker-driven approaches to

Table 3. Clinical implications and future directions for ALA in hepatocellular carcinoma therapy

Challenge/Aspect	Current status	Potential solutions/Strategies	References
Bioavailability	Limited systemic exposure with oral administration	Developing novel delivery systems (e.g., liposomes, nanoparticles)	89
Pharmacokinetics	Insufficient data on optimal dosing and toxicity	Conducting pharmacokinetic studies to determine optimal dosing in cancer patients	86
Combination therapies	Limited data on ALA with other HCC treatments	Investigating synergy with therapies like sorafenib and immune checkpoint inhibitors	107
Biomarker identification	Lack of patient-specific biomarker data	Developing biomarker-driven approaches to identify ALA therapy responders	111
Clinical trial design	Few clinical trials in HCC patients	Designing well-controlled clinical trials focusing on bioavailability and efficacy	112
Formulation variability	Potential inconsistency in natural compound formulations	Standardizing formulations for reproducibility in clinical settings	112

Abbreviations: ALA: Alpha lipoic acid; HCC: Hepatocellular carcinoma; mTOR: Mammalian target of rapamycin.

identify patients who may benefit most from ALA-based therapies. In addition, challenges related to the design of clinical trials for natural compounds, such as variability in formulation and dosing, must be addressed to ensure reproducibility and reliability of results.¹¹²

7.3. Exploring other natural compounds targeting AMPK-p53 axis

ALA is not the only natural compound with the potential to target the AMPK-p53 axis in HCC. Other natural compounds, such as curcumin and resveratrol, have also been shown to activate AMPK and inhibit cancer cell proliferation and metastasis. Exploring the synergistic effects of these compounds, either alone or in combination with ALA, may provide new avenues for developing multi-targeted therapies for HCC and other cancers.¹¹³

8. Conclusion

The review highlights the significant potential of ALA as a therapeutic agent in HCC, particularly focusing on its ability to inhibit metastasis by modulating the AMPK-p53 axis. Dual action of ALA in activating AMPK and p53 offers a promising approach to suppress critical pathways involved in HCC progression, such as mTOR and EMT. This not only facilitates apoptosis but also limits cancer cell migration and invasion. However, despite promising preclinical studies, the clinical application of ALA remains limited by challenges such as poor bioavailability and insufficient pharmacokinetic data in humans. The relevance of these findings lies in the potential to develop more effective combination therapies targeting both tumor proliferation and metastatic spread. Future research should focus on optimizing ALA formulation, improving systemic delivery, and conducting biomarker-driven clinical trials to fully realize its therapeutic potential.

To advance the application of ALA in HCC treatment, it is recommended that further research explores strategies to improve the bioavailability and pharmacokinetics of ALA through novel drug delivery systems or formulation improvements. In addition, combination therapies involving ALA and standard treatments like tyrosine kinase inhibitors (e.g., sorafenib) or immune checkpoint inhibitors should be investigated to enhance therapeutic efficacy. Biomarker-driven approaches can help identify specific patient populations that would respond most favorably to ALA-based therapies. Finally, well-designed clinical trials are crucial to translating the promising preclinical findings into effective clinical interventions, addressing both ALA's dosing parameters and its long-term safety profile in cancer patients.

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Conflict of interest

The author declares that he has no competing interests.

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