# Role of MicroRNAs Induced by Chinese Herbal Medicines Against Hepatocellular Carcinoma: A Brief Review

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## Abstract

MicroRNAs (miRNAs) are highly conserved, noncoding small RNAs that regulate gene expression, and consequently several important functions including early embryo development, cell cycle, programmed cell death, cell differentiation, and metabolism. While there are no effective treatments available against hepatocellular carcinoma (HCC), some Chinese herbal medicines have been shown to regulate growth, differentiation, invasion, and metastasis of HCC. Many studies have shown that Chinese herbal medicines regulate the expression of miRNAs and this may be associated with their ability to control the development of HCC. In this article, the effects of Chinese herbal medicines on the expression of miRNAs and their functions in the regulation of HCC have been reviewed and discussed. miRNAs such as miRNA-221 and miRNA-222 mediated by Chinese herbal medicines may be good biomarkers and therapeutic targets for HCC.

## Keywords

miRNAs, Chinese herbal medicines, hepatocellular carcinoma

## Introduction

Liver cancer is one of the most common human malignant tumors, ranking in top 3 of the world's cancer mortality rate.[1,2] It has been reported that 50% of liver cancer cases and deaths in the world take place in China. It was estimated that about 466 000 new cases of liver cancer were diagnosed in China and 422 000 Chinese died from cancer in 2015, corresponding to over 158 cancer deaths on average per day.[3] Approximately 70% to 90% of liver cancers are hepatocellular carcinoma (HCC) worldwide.[4]

The pathogenesis of HCC has not been fully understood. About 80% of HCC are caused by chronic infection with hepatitis B virus or hepatitis C virus.[5] Obesity, type 2 diabetes, and nonalcoholic fatty liver disease may also contribute to HCC development.[6] Several key cancer genes such as *TP53, WNT-CTNNB1*, and cell cycle–related genes could play an important role in HCC pathogenesis.[7] Although a lot of effort has been devoted, there are currently no effective systemic treatments available for HCC.[8,9]

MicroRNAs (miRNAs) are highly conservative and endogenic noncoding small RNAs. miRNAs have various forms in the genome, including single copy, multiple copy, gene cluster, and so on. They are mostly located in the gene compartment.[10] They are transcribed independently from other genes. miRNAs play an important role in early embryo development, cell cycle regulation, programmed death, cell differentiation, and metabolism.[11,12]

A number of studies have shown that miRNAs are closely related to cancer development. miRNAs can regulate the proliferation, apoptosis, invasion, and metastasis of cancer cells.[13] Recent studies have shown that miRNAs play a critical role in the pathogenesis of HCC, and may be used as biomarkers and therapeutic targets for diagnosis and treatment of HCC.[8] Chinese herbal medicines not

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**Table 1.** Function of Chinese Herbal Medicines in Hepatocellular Carcinoma.

| Chinese Herbal Medicine | Active Compound | Type of Compound | Cell Samples Tested | Function | Reference |
|---|---|---|---|---|---|
| *Coptis chinensis* | Berberine, evodiamine | Alkaloid | HepG2 | Inhibit cell growth in vitro and in vivo | Chou et al[24] |
| *Sophora flavescens* | Matrine | Alkaloid | H22 | Inhibit proliferation and induce apoptosis in vitro and in vivo | Ma et al[25] |
| *Tripterygium wilfordii* | Triptolide | Diterpenoid epoxide | HepG2 | Increased cellular sensitivity to cisplatin and 5-FU in vivo and in vitro | Li et al[26] |
| *Dendrobium huoshanense* | Glycoproteins | Glycoprotein | HepG2 | Inhibit cell growth | Deng et al[19] |
| *Vitex negundo* | Evn-50 | Lignan | SMMC-7721 | Inhibit cell cycle | Xin et al[20] |
| *Salvia chinensis* | Protocatechu-aldehyde | Phenolic aldehyde | PLC/PRF/5 | Inhibit cell cycle, cell proliferation, metastasis in vivo | Wang et al[14] |
| *Salvia miltiorrhiza* | Tanshinones | Quinone | HepG2 | Inhibit cell cycle, induce apoptosis | Lee et al[21] |
| *Panax ginseng* | Ginsenoside | Saponine | SMMC-7721 | Block cell cycle, induce differentiation | Zheng et al[18] |
| Platycodonis radix | Platycodin D | Saponine | HepG2, Hep3B | Inhibit proliferation and migration, induce apoptosis | Li et al[22] |
| *Artemisia annua* | Artemisinin | Sesquiterpene lactone | SMMC-7721 | Inhibit cell growth, induce apoptosis | Deng et al[23] |

only play a role in the growth, apoptosis, differentiation, invasion, and metastasis of HCC cells, but also are involved in the regulation of miRNA expression and functions.[2,14,15] Following a search through the PubMed, Science Citation Index, and EMBASE databases, this article reviewed the current research progress of Chinese herbal medicines in the control of HCC development through specific miRNAs, which provide new effective markers and targets for the diagnosis and treatment of HCC.

## Effects of Chinese Herbal Medicines on HCC

It has been shown that Chinese herbal medicines are often used and may be beneficial in the treatment of HCC.[2,16,17] This is because Chinese herbal medicines can inhibit cell proliferation and induce the differentiation of HCC cells to normal cells (Table 1). For instance, ginsenoside Rh2 from *Panax ginseng* CA Mey blocked human HCC cell line SMMC-7721 at G1/G0 phase and induced cell differentiation tending to normal phenotype.[18] Glycoproteins purified from *Dendrobium huoshanense* inhibited the cell growth of human HCC cell line HepG2.[19] Evn-50, a lignan compound mixture, isolated from *Vitex negundo*, arrested the cell cycle of SMMC-7721 cells at G2/M phase.[20] Tanshinones, abietane-type diterpene quinones, extracted from the roots of *Salvia miltiorrhiza*, inhibited the cell cycle and induced apoptosis of HepG2 cells.[21]

The molecular mechanisms of Chinese herbal medicines in HCC were also studied. It has been reported that platycodin D isolated from Platycodonis radix upregulated the expression of cleaved poly ADP-ribose polymerase and Bax and downregulated the expression of survivin in HCC cell lines Hep3B and HepG2. Thus, platycodin D could inhibit proliferation, migration, and invasion and induce apoptosis of both Hep3B and HepG2 cells.[22] Artemisinin extracted from *Artemesia annua* L inhibited cell growth and proliferation and induced apoptosis of SMMC-7721 cells by means of increased concentration of ferrous iron in cancer cells.[23] Therefore, platycodin D and artemisinin may be used as potential anticancer drugs in the treatment of HCC.

Studies using mouse model also showed that Chinese herbal medicines may be beneficial in the treatment of HCC. Alkaloids berberine and evodiamine isolated from *Coptis chinensis* could suppress HepG2 cell growth both in vitro and in mouse model.[24] Chinese herbal medicine *Salvia chinensis* Benth and its active compound protocatechualdehyde were found to inhibit Wnt/β-catenin pathway, and thus block the cell cycle and proliferation of human HCC cell line PLC/PRF/5, and suppress HCC metastasis in mice.[14] Matrine purified from *Sophora flavescens* Ait suppressed the proliferation and induced apoptosis of murine hepatocellular carcinoma H22 cells both in vitro and in mice.[25]

In addition, triptolide isolated from *Tripterygium wilfordii* could increase cellular sensitivity of HCC cells to chemotherapeutic drugs such as cisplatin and 5-fluorouracil both in vivo and in vitro by means of induced Bax expression, inhibited Bcl-2 expression, increased intracellular reactive oxygen species production, and enhanced caspase-3 activity.[26] Therefore, triptolide may be used in

combination therapy with chemotherapeutic drugs for the effective treatment of HCC.

## Effects of Chinese Herbal Medicines on miRNA Expression

As stated, Chinese herbal medicines may have some benefits in the treatment of HCC. However, clinical evidence for the effective treatment of Chinese herbal medicines in HCC is seldom available due to unclear mechanisms induced by Chinese herbal medicines in HCC therapy.[27] It has been shown that Chinese herbal medicines may target reactive oxygen species, affect the expression of genes associated with the control of cell cycle, apoptosis and migration, and regulate the immune system, leading to the inhibition of HCC development.[16] Chinese herbal medicines may also play a role in the regulation of signaling pathways such as PI3K/AKT, NF-κB, and MAPK signaling pathway.[28] For instance, the Chinese herbal medicine *Salvia chinensis* Benth targeted WT1 protein, suppressed Wnt/β-catenin pathway, and thus inhibited HCC cell growth and metastasis both in vitro and in mouse tumor model.[14] The mechanisms of Chinese herbal medicine function in the treatment of different cancers are still not clearly understood.[29,30] Recent studies have documented miRNAs may play an important role in cancer development.[31] Thus, it is interesting to understand the effects of Chinese herbal medicines on miRNA expression and functions.

It has been reported that ginsenoside Rb1 purified from *P ginseng* inhibited miRNA-25 expression, and thus suppressed hypoxia-induced E-cadherin downregulation and vimentin upregulation, inhibited cell migration, and blocked epithelial-mesenchymal transition (EMT) in SKOV3 and 3AO human ovarian cancer cells, suggesting that ginsenoside Rb1 could be used in the treatment of ovarian cancer.[32] Cordycepin, an adenosine analogue isolated from *Cordyceps militaris*, downregulated miRNA-21 expression, and thus induced apoptotic cell death and inhibited cell migration in renal cell carcinoma Caki-1 cell line.[33] Therefore, Chinese herbal medicines such as ginsenoside Rb1 and cordycepin may have antitumor activity in a broad spectrum of cancer types through the regulation of specific miRNAs.

Chinese herbal medicines may regulate the expression of specific miRNAs and thus play a role in the pathogenesis of other diseases. For example, resveratrol extracted from *Polygonum cuspidatum* and grapes downregulated miRNA-155. miRNA-155 could target suppressor of cytokine signaling 1, an inhibitor of signal transducer and activator of transcription 1 (STAT1) and STAT3 in lipopolysaccharide stimulated RAW264.7 murine macrophages. Thus, resveratrol suppressed the production of tumor necrosis factor-α and interleukin 6, inhibited the expression of STAT1 and STAT3, and decreased the phosphorylation of mitogen-activated protein kinases (MAPKs).[34] The results suggested that resveratrol might have anti-inflammatory effects and be used in the treatment of inflammatory diseases. Because inflammation drives several models of tumorigenesis, it is likely that such anti-inflammatory properties of herbal medicines may help prevent certain types of cancer.

Salvianolic acid A (Sal A), a polyphenol compound isolated from *S miltiorrhiza*, significantly increased miRNA-101 expression and miRNA-101 targeted Cul3 protein in rat brain microvascular endothelial cells, resulting in the improved recovery of neurological function.[35] Calycosin, an isoflavone isolated from Radix Astragali, upregulated miRNA-375 in cerebral ischemia/reperfusion animal models. Therefore, calycosin significantly reduced the infarcted volume and the brain water content, and improved the neurological deficit. The results indicated that calycosin may have neuroprotective effects.[36] Dihydromyricetin, a flavonoid extracted from *Ampelopsis grossedentata*, downregulated miRNA-34a expression, and thus upregulated SIRT1, downregulated mTOR signal pathways, inhibited apoptosis, and rescued impaired autophagy of neurons in hippocampus tissue in the model rats with D-gal-induced brain aging, suggesting that dihydromyricetin improved aging-related diseases. In addition, dihydromyricetin has other multiple pharmacological functions including anti-inflammatory, antioxidative, and anticancer functions.[37] Therefore, Chinese herbal medicines may play a role in the control of both cancer and neurological diseases.

Puerarin, an isoflavone extracted from Radix puerariae inhibited miRNA-22, and miRNA-22 targeted caveolin-3. Therefore, puerarin improved myofibril array and sarcomeres formation, and significantly facilitated t-tubules development in embryonic stem cell-derived cardiomyocytes, suggesting that puerarin may play a role in cardiomyogenesis.[38] Tanshinone IIA, extracted from *S miltiorrhiza*, upregulated the expression of miRNA-133 and stress-activated protein kinase MAPK ERK1/2, and thus inhibited apoptosis and increased cell resistance to hypoxic in cultured rat cardiomyocytes, suggesting that tanshinone IIA may be used in the treatment of cardiovascular disorders.[39]

It has been reported that triptolide isolated from *T wilfordii* upregulated miRNA-137, and miRNA-137 targeted Notch1, leading to inhibition of extracellular matrix protein expression in human renal mesangial cells and a positive role in the anti-glomerulosclerosis.[40]

Based on the evidence presented above, it is likely that Chinese herbal medicines can regulate specific miRNAs and play a role in the control of biological functions (Table 2). These studies also indicated that Chinese herbal medicines may control of HCC pathogenesis by means of regulation of miRNA expression.

**Table 2.** Regulation of Chinese Herbal Medicine in miRNA Expression and Function.

| Chinese Herbal Medicine | Active Compound | Type of Compound | miRNA | miRNA Expression | Function | Reference |
|---|---|---|---|---|---|---|
| *Cordyceps militaris* | Cordycepin | Adenosine analogue | miRNA-21 | Down | Antitumor | Yang et al[33] |
| *Tripterygium wilfordii* | Triptolide | Diterpenoid epoxide | miRNA-137 | Up | Anti-glomerulosclerosis | Han et al[40] |
| *Ampelopsis grossedentata* | Dihydromyricetin | Flavonoid | miRNA-34a | Down | Anti-brain aging | Kou et al[37] |
| Radix Astragali | Calycosin | Isoflavone | miRNA-375 | Up | Neuroprotection | Wang et al[36] |
| *Radix puerariae* | Puerarin | Isoflavone | miRNA-22 | Down | Cardiomyogenesis | Wang et al[38] |
| *Polygonum cuspidatum* | Resveratrol | Polyphenol | miRNA-155 | Down | Anti-inflammation | Ma et al[34] |
| *Salvia miltiorrhiza* | Salvianolic acid A | Polyphenol | miRNA-101 | Up | Recovery of neurological function | Yu et al[35] |
| *Salvia miltiorrhiza* | Tanshinone IIA | Quinone | miRNA-133 | Up | Treatment of cardiovascular disorders | Zhang et al[39] |
| *Panax ginseng* | Ginsenoside Rb1 | Saponine | miRNA-25 | Down | Antitumor | Li et al[32] |

## Potential Role of Chinese Herbal Medicine–Mediated miRNAs in HCC

It appears that Chinese herbal medicines can affect the expression of specific miRNAs and thus are associated with the pathogenesis of cancer and other diseases (Table 2). The specific miRNAs affected by Chinese herbal medicines may play a role in HCC development.

It has been reported that miRNA-21 was significantly upregulated in HCC and could be used as a novel biomarker of HCC.[41,42] Cordycepin isolated from *Cordyceps militaris* could downregulate miRNA-21 expression, and induce apoptotic cell death and inhibit cell migration in renal cell carcinoma cells.[33] It is possible that cordycepin may suppress HCC development through the downregulation of miRNA-21. Similarly, miRNA-25 was also significantly upregulated in HCC clinical samples and stimulated HCC cell growth, migration, and invasion.[43] Ginsenoside Rb1 purified from *Panax ginseng* was found to inhibit miRNA-25 expression, suppress cell migration, and block EMT in SKOV3 and 3AO human ovarian cancer cells.[32] Thus, it is assumed that ginsenoside may inhibit miRNA-25 expression and so suppress HCC development. It has been shown that miRNA-34a expression was upregulated in hypoxic HCC tissue as compared with the surrounding tissue.[44] Dihydromyricetin extracted from *Ampelopsis grossedentata* downregulated miRNA-34a expression and had anticancer functions.[37] Thus, dihydromyricetin may suppress miRNA-34a expression and inhibit HCC development. In addition, miRNA-155 has been shown to be upregulated in HCC patients; it promotes tumor growth, cellular invasion and migration in vitro, and is a well-known oncomiR in various cancers.[45-48] Resveratrol extracted from *P cuspidatum* and grapes downregulated miRNA-155.[34] It is possible that resveratrol may inhibit miRNA-155 expression and thus play a role in the control of HCC development. These facts indicate that upregulated miRNA-21, miRNA-25,

miRNA-34a, and miRNA-155 in HCC patients may be used as targets for effective treatment of HCC.

In contrast, serum level of miR-101 was significantly lower in HCC patients than in healthy controls.[41] Sal A isolated from *S miltiorrhiza*, however, significantly increased miRNA-101 expression.[35] The results suggested that Sal A could upregulate miRNA-101 and hence inhibit HCC development. It has been reported that miRNA-137 was significantly downregulated in HCC. Overexpression of miRNA-137 suppressed cell proliferation, migration, and invasion; however, the inhibition of miRNA-137 expression promoted HCC cell growth in vitro.[49] It has been reported that triptolide isolated from *T wilfordii* upregulated miRNA-137.[40] Therefore, triptolide may increase miRNA-137 expression and inhibit HCC development. These studies show that downregulated miRNA-101 and miRNA-137 in HCC patients may potentially be used as targets for HCC treatment.

miRNA-22 was found to be downregulated in HCC and miRNA-22 overexpression inhibited HCC cell growth, invasion, and metastasis both in vitro and in vivo.[50-52] Puerarin extracted from Radix puerariae inhibited miRNA-22 expression.[38] Therefore, puerarin may regulate miRNA-22 expression and thus affect HCC development. Recent studies showed that miRNA-133 expression was significantly downregulated in human lung adenocarcinoma specimens and cell lines as compared with the normal controls. Further study discovered that miRNA-133 significantly suppressed metastasis of lung adenocarcinoma cells in vitro.[53] miRNA-133 expression was also significantly downregulated in glioma tissues and cell lines. In vitro studies found that miRNA-133 overexpression could inhibit cell growth and invasion of glioma cells dramatically.[54] Other studies also demonstrate that miRNA-133 has anticancer functions.[55] These results suggest that miRNA-133 may play a role in HCC development. Tanshinone IIA extracted from *S miltiorrhiza* upregulated miRNA-133.[39] Therefore, Tanshinone

**Table 3.** Expression and Function of miRNAs Regulated by Chinese Herbal Medicines in Hepatocellular Carcinoma.

| Chinese Herbal Medicine | Active Compound | Type of Compound | miRNA | miRNA Expression | Function | Reference |
|---|---|---|---|---|---|---|
| *Corydalis yanhusuo* | Corydaline | Alkaloid | let-7a | Up | Inhibit proliferation | Zhang et al[57] |
| *Corydalis yanhusuo* | Corydaline | Alkaloid | miRNA-221 and miRNA-222 | Down | Inhibit proliferation | Zhang et al[57] |
| *Andrographis paniculate* | Andrographolide | Diterpenoid | miRNA-222-3p, miRNA-106b-5p, miRNA-30b-5p, and miRNA-23a-5p | Up | Inhibit tumor growth | Lu et al[59] |
| *Salvia miltiorrhiza* | Tanshinones | Quinone | miRNA-30b | Down | Antihepatocarcinomic and liver cancer treatment | Ren et al[60] |
| *Polygonum cuspidatum* | Resveratrol | Polyphenol | miRNA-151 | Down | Inhibit proliferation and induce apoptosis | Xu et al[58] |

IIA could potentially increase miRNA-133 expression and be involved in the control of HCC development. Additionally, miRNA-375 was found to be in hypermethylation and downregulation status in HCC cell lines.[56] Calycosin isolated from Radix Astragali could upregulate miRNA-375 expression in cerebral ischemia/reperfusion animal models.[36] It is possible that calycosin may regulate miRNA-375 expression and control HCC development. The assumptions will be required to be confirmed by further investigations.

## Role of miRNAs Regulated by Chinese Herbal Medicines in HCC

Limited studies have shown that Chinese herbal medicines may regulate the expression of specific miRNAs and thus play a role in the development and treatment of HCC (Table 3). It has been reported that corydaline, a natural alkaloid isolated from *Corydalis yanhusuo*, upregulated let-7a and downregulated miRNA-221 and miRNA-222, leading to the inhibition of HCC HepG2 cell proliferation.[57] Resveratrol reduced the expression of miRNA-151 and thus inhibited cell proliferation and induced apoptosis of HepG2 cells.[58] Besides, andrographolide, a labdane diterpenoid isolated from *Andrographis paniculata*, upregulated the expression of miRNA-23a-5p, miRNA-30b-5p, miRNA-106b-5p, and miRNA-222-3p, targeted genes involved in a variety of signaling pathways in cancer, MPAKs and focal adhesion, and thus inhibited HCC tumor growth both in vitro and in mice. Thus, andrographolide regulated the expression of specific miRNAs and downstream signals, which may lead to the inhibition of HCC cell growth.[59] Tanshinone IIA extracted from *S miltiorrhiza* downregulated miRNA-30b, and thus arrested cell cycle at the G1 phase and induced apoptosis of HepG2 cells. The results suggested that tanshinone IIA might have anti-hepatocarcinomic properties through regulation of miRNA and be effectively used in the treatment of HCC.[60]

## Mechanisms of Function of miRNAs Regulated by Chinese Herbal Medicines in HCC

It has been becoming clear that Chinese herbal medicines may regulate the expression of specific miRNAs in HCC (Table 3). Studies on the mechanisms of function of miRNAs have great implications in understanding the roles of specific miRNAs in HCC pathogenesis. It has been reported that miRNA-23a-5p target TLR2, and thus inhibited the expression of MyD88 and NF-κB in RAW264.7 cells.[61] TLR2 was upregulated in HCC tumor tissue and knocking down TLR2 expression by RNA interference blocked the proliferation of HepG2 cells.[62] Myd88 expression was found to be upregulated in HCC and the enhanced expression of Myd88 could promote the proliferation and metastasis of HCC both in vitro and in vivo.[63] NF-κB promotes HCC cell proliferation, migration, metastasis, and progression.[64,65] Therefore, it is possible that miRNA-23a-5p induced by andrographolide isolated from *A paniculata* may inhibit HCC growth and development through TLR2/MyD88/NF-κB pathway.

The expression levels of miRNA-30b-5p decreased dramatically in renal cell carcinoma, miRNA-30b-5p targeted G-protein subunit α-13 (GNA13), and thus inhibited cell proliferation, metastasis, and EMT of renal cell carcinoma.[66] It has been reported that GNA13 stimulated G1/S cell cycle transition, proliferation, and tumorigenicity through upregulation of c-Myc, activation of AKT and ERK activity, suppression of FOXO1 activity, upregulation of cyclin-dependent kinase regulator cyclin D1, and downregulation of cyclin-dependent kinase inhibitor p21Cip1 and p27Kip1 in gastric cancer.[67] The results indicated that miRNA-30b-5p induced by andrographolide isolated from *A paniculata* might target GNA13 and its downstream molecules and thus inhibit HCC development.

It has been reported that miRNA-151 targeted RhoGDIA, a putative metastasis suppressor, and thus activated Rac1, Cdc42, and Rho GTPases, leading to increased HCC cell

migration and invasion in vitro and in vivo.[68] The facts suggested that miRNA-151 down-regulated by resveratrol could target and thus inhibit HCC cell proliferation and induce HCC cell apoptosis.

It was found that a higher expression of miRNA-221 was associated with poor survival in patients with colorectal cancer and miRNA-221 promoted colorectal cancer cell proliferation. Tumor protein 53-induced nuclear protein 1 (TP53INP1) was a direct target of miRNA-221.[69] Therefore, miRNA-221 down-regulated by corydaline isolated from *C yanhusuo* may target TP53INP1, and thus inhibit HCC cell proliferation.

miRNA-222 was upregulated in gastric cancer cells and targeted growth arrest-specific transcript 5 (GAS5), a tumor suppressor. GAS5 overexpression increased PTEN protein level and decreased p-Akt and p-mTOR protein levels in gastric cancer cells.[70] Thus, miRNA-222 downregulated by corydaline isolated from *C yanhusuo* may target GAS5 and thus inhibit HCC cell proliferation through the PTEN/Akt/mTOR pathway. Besides, miRNA-222 targeted the p53 upregulated modulator of apoptosis (PUMA) and downregulation of miRNA-222 induced apoptosis of adenoid cystic carcinoma cells.[71] The fact suggested that miRNA-222 may also target PUMA and affect HCC cell growth.

It has been reported that let-7a was significantly down-regulated in papillary thyroid carcinoma tissues and thyroid cancer cell lines. Let-7a targeted v-AKT murine thymoma viral oncogene homologue 2 (AKT2) and thus inhibited the cell proliferation, migration, and invasion of papillary thyroid carcinoma.[72] The expression of let-7a was dramatically decreased in cervical cancer tissues and cancer cell lines; let-7a directly suppressed the expression of pyruvate kinase muscle isozyme M2 (PKM2) target gene and thus inhibited cell proliferation, migration, and invasion, and enhanced of cancer cells in vitro and in vivo.[73] Furthermore, let-7a could target high-mobility group AT-hook 2 (HMGA2) and thus inhibit cell proliferation and metastasis of pancreatic cancer cells.[74] Therefore, it is possible that let-7a upregulated by corydaline isolated from *C yanhusuo* may target AKT2, PKM2, and HMGA2, and inhibit HCC development.

## Prospects

Chinese herbal medicines have been used in the treatment of HCC. The effectiveness of Chinese herbal medicines in the treatment of HCC, however, is still elusive. Further studies will be required for the successful application of Chinese herbal medicines in HCC therapy. Chinese herbal medicines always have side effects due to the complex mixture of compounds, resulting in the limitations of Chinese herbal medicines in clinical applications.[75,76] Therefore, the efforts should be focused on the purification and identification of active compounds from Chinese herbal medicines. The extensive investigations on the functions and underlying mechanisms of active compounds purified from Chinese herbal medicines in HCC cells in vitro will be required to accomplish that goal. The effectiveness, pharmacokinetics, and safety of active compounds from Chinese herbal medicines should be tested in animal models for drug development and in the effective treatment of HCC. It will be also necessary to explore the effects of active compounds from Chinese herbal medicines on the expressions, functions, and underlying mechanisms of specific miRNAs in HCC. The identification of miRNA involved in the efficacy of herbal medicines against HCC could also lead to the development of new therapeutics that target such miRNA directly. Furthermore, the studies on the functions and underlying mechanisms of active compounds from Chinese herbal medicines in the regulation of antitumor immunity in vivo will be needed. It is expected that novel effective drugs can be developed from Chinese herbal medicines for HCC treatment in the near future.

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