Review Article

Hepigenetics: A Review of Epigenetic Modulators and Potential Therapies in Hepatocellular Carcinoma

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Received 11 August 2020; Revised 13 October 2020; Accepted 5 November 2020; Published 24 November 2020

Academic Editor: Junyan Tao

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Hepatocellular carcinoma is the fifth most common cancer worldwide and the second most lethal, following lung cancer. Currently applied therapeutic practices rely on surgical resection, chemotherapy and radiotherapy, or a combination thereof. These treatment options are associated with extreme adversities, and risk/benefit ratios do not always work in patients' favor. Anomalies of the epigenome lie at the epicenter of aberrant molecular mechanisms by which the disease develops and progresses. Modulation of these anomalous events poses a promising prospect for alternative treatment options, with an abundance of felicitous results reported in recent years. Herein, the most recent epigenetic modulators in hepatocellular carcinoma are recapitulated on.

1. Introduction

Hepatocellular carcinoma (HCC) is a notoriously aggressive cancer with high global prevalence rates and is the next most common perpetrator of cancer-related death following pulmonary carcinomas, with annual mortality rates of the order of 800,000 deaths [1]. HCC develops in a backdrop of a chronic liver disease that ultimately results in liver fibrosis and cirrhosis, which are consequential HCC risk factors. Hepatitis C and B, aflatoxins, alcoholic liver disease, and nonalcoholic steatohepatitis are all commonly encountered chronic inflammatory hepatopathologies that predispose to HCC. Depending on the etiology, disparate molecular dysregulation patterns arise, all converging on promoting malignancy. The loss of cell cycle restraints, incapacity to senesce, and disarrayed apoptosis [2] are among such dysregulated mechanisms, which could well be the result of genetic as well as epigenetic alterations.

The epigenome constitutes heritable features of the genetic material out with the DNA sequence. Specific epigenetic patterns are important for the maintenance of cellular integrity and gene expression patterns associated with health. In this capacity, the epigenetic fingerprint functions to guarantee proper and timely expression of genetic information,

and its alteration aggravates pernicious cellular changes, many of which predispose to cancer [3]. Herein, a compendium of the most recent work addressing epigenetic modulators in the context of HCC is presented.

1.1. What Is Epigenetics? Epigenetics is a term that was first coined by Conrad Waddington, and it literally means “above genetics” [4]. It entails changes to cellular phenotypes, which are not dependent on alterations of the genetic code (DNA sequence). However, unanimity regarding the definition of epigenetics has thus far been elusive, and debates in this regard have been inconclusive at best [5].

As previously mentioned, the most recognized of epigenetic mechanisms involve chromatin remodeling. Chromatin is the macromolecule by virtue of which the genetic material can be packed inside cells' nuclei. It is composed of nucleosomes: DNA wound around histone protein octamers. In its compact form, the heterochromatin, the genetic material is relatively inaccessible for replication and the genes within are largely silent. The euchromatin on the other hand is a relaxed form of chromatin where the DNA is more accessible and genes are more or less actively expressed [5]. It can thus be easily concluded that regulation of chromatin condensation plays a role in regulating gene expression and the

resulting phenotypes. Chromatin-modifying enzymes are key players in effecting such restructuring and subsequent modifications to DNA and the histone scaffolding on which it is wound.

CpG islands are clusters of CpG dinucleotides predominantly found in the promoter regions of genes. Generally, methylation of the 5-carbon in the cytosine of these CpG islands shields the promoter from the transcription machinery to the end result of a controlled gene expression. On the other hand, demethylation of these regions within gene promoters allows for the recruitment of the transcription machinery and the gene is essentially “on.” Such functionality is predominantly reserved for DNA methyltransferases. That being said, promoters containing CpG islands account for only 70% of the promoters in the genome. Interaction with the remaining 30% is orchestrated by modifications to the histone proteins, regulated—to a large extent—by histone deacetylases [5]. The disruption of these mechanisms can thus lead to aberrations in gene expression, which in many cases can initiate or promote oncogenesis. For example, the promoters of genes, which are normally turned off, are usually found hypomethylated in cancer.

1.2. Epigenetic Modulators. Options for epigenetic therapies in HCC can be enumerated as follows: inhibitors of DNA methyltransferases, regulators of histone methyltransferases, demethylases, acetyltransferases, and—most prominently—deacetylases. Another major class of epigenetic modulators is represented in noncoding RNAs. Below, the most eminent and clinically established classes are explored comprehensively to afford an encyclopedic overview of the current status of epigenetic recourse for HCC therapy. However, due to scarcity of data, several agents such as tacedinaline, romidepsin, some helicases, and other enzymes viz. acireductone dioxygenase 1 are not discussed.

2. DNA Modifications

2.1. DNA Methyltransferases (DNMTs). The implication of epigenetic changes in HCC, specifically aberrant patterns of DNA methylation, has recently been recognized as a primary contributor to disease onset and progression [6]. As a consequence of such epigenetic anomalies, key tumor suppressors may be silenced or oncogenes activated, resulting in the initiation of tumorigenesis. DNA methylation is mediated by a conserved class of catalytic proteins known as *DNA methyltransferases* (DNMTs). DNMTs are key players of the epigenome. DNMTs come in two primary categories, maintenance (DNMT1) and *de novo* DNMTs (DNMT3a and DNMT3b) [7]. Although the distinction is not absolute, it does hold contemporarily. *DNMT1*, *DNMT3a*, and *DNMT3b* function by catalyzing the transfer of a methyl group from S-adenosyl-L-methionine, the universal methyl donor to a 5'-cytosine on DNA [8]. Moreover, several other DNMTs do exist (such as *DNMT2* and *DNMTL*); however, they remain relatively undefined despite having demonstrated a role in HCC [9].

Despite the widely suggested distinction that *DNMT1* functions as the maintenance methyltransferase and *DNMT3a*

and *DNMT3b* mediate *de novo* methylation (predominantly during embryonic development), the notion has been challenged as of late, with *DNMT1* recognized as a contributor to *de novo* methylation while maintenance functions are mediated by *DNMT3a* and *DNMT3b* in concert with *DNMT1* [10]. Notwithstanding the above-mentioned classification, these enzymes do not function individually and their interaction is crucial to the creation and maintenance of appropriate methylation patterns. The alteration of such coordination has in fact been associated with cancer development [11].

2.2. DNMT1. *DNMT1* is the most common subtype in adult cells [12]. Normally, *DNMT1* functions to maintain methylation patterns of CpG sites within promoters. This is achieved by *DNMT1* accessing hemi-methylated DNA during replication, priming the daughter unmethylated strand for methylation. However, anomalous DNMT-mediated methylation jeopardizes typical gene expression patterns as a result of increased or decreased accessibility of CpG-rich promoters. HCC and its adjacent tissues have demonstrated notably different DNA methylation patterns [6]. Where the noncancerous neighboring tissues display uniform and stable methylation patterns, HCC exhibits a marked heterogeneity. According to the reported results, HCC tissues manifest reduced methylation of CpG regions. Table 1 shows a snippet of the reported signature of methylated genes in HCC, which is reportedly capable of differentiating HCC samples from neighboring tissues. A former study showed that DNA methylation of CpG island-associated promoters silenced gene expression and defined 222 drivers of epigenetic changes exhibiting this negative correlation. A preponderance of these candidate drivers was found to be enriched in inflammatory responses, a number of metabolic processes, and oxidation-reduction reactions. A set of reliable and robust candidates was also defined (Table 1).

Neurofilament, heavy polypeptide (NEFH) and *sphingomyelin phosphodiesterase 3 (SMPD3)* were also defined as tumor suppressor genes that were hypermethylated and silenced in HCC [13]. The results obtained from the gain of function experiments revealed diminished cellular proliferation, whereas those of knockdowns restored tumor invasiveness and migratory capacities. Conversely, hypomethylation of the fetal promoters of the oncogene, *IGF2*, gave way to its overexpression, imparting virulent phenotypes [14]. DNA methylation has also been inculpated in the dysregulation of several long noncoding RNAs (lncRNAs), which have been awhile associated with HCC. The histone methyltransferase *enhancer of zeste homolog 2 (EZH2)*, which catalyzed the trimethylation at lysine 27 of histone H3, has been proven to silence *TCAM1P-004* and *RP11-598D14.1*: two tumor-suppressing long noncoding RNAs [15]. This has been supposed to be assisted by *Yin Yang 1 (YY1)*, which purportedly aids in recruiting *EZH2* to promoters of target genes [16]. The downregulation of these lncRNAs correlated with tumor progression owing to the inhibition of their moderation of the *mitogen-activated protein kinase (MAPK)*, *tumor protein p53 (p53)*, and *hypoxia-inducible factor 1-alpha (HIF1-α)* pathways [15]. As would be expected, upregulation of histone methyltransferases might just be the driver for neoplastic

TABLE 1: Aberrant methylation patterns in hepatocellular carcinoma (HCC). A comprehensive list of genes, which were dysregulated in HCC due to aberrant methylation patterns.

Gene	Methylation pattern	Ref.
<i>ACSL4</i>	Hypomethylation	
<i>ALDH3A1</i>	Hypomethylation	[217]
<i>APOA5</i>	Hypermethylation	
<i>CLDN15</i>	Hypomethylation	
<i>CDKN2A</i>	Hypermethylation	[6]
<i>CYP7A1</i>	Hypomethylation	[217]
<i>DEFB119</i>	Hypomethylation	
<i>DPP6</i>	Hypomethylation	[6]
<i>ENDOD1</i>	Hypermethylation	
<i>EZR</i>	Hypermethylation	[217]
<i>GLUL</i>	Hypomethylation	
<i>GZMB</i>	Hypomethylation	[6]
<i>MIR21</i>	Hypomethylation	[218]
<i>Myo1g</i>	Hypermethylation	[219]
<i>NEFH</i>	Hypermethylation	[13]
<i>NKX3-2</i>	Hypermethylation	
<i>NDRG2</i>	Hypermethylation	[6]
<i>PDE1A</i>	Hypomethylation	
<i>PHYHD1</i>	Hypermethylation	[217]
<i>PRH2</i>	Hypermethylation	[6]
<i>RASSF1A</i>	Hypermethylation	[220]
<i>RP11-598D14.1</i>	Hypermethylation	[15]
<i>SCAND3</i>	Hypermethylation	[219]
<i>SPP1</i>	Hypomethylation	[217]
<i>SPRR2A</i>	Hypomethylation	[6]
<i>SLC25A47</i>	Hypermethylation	[6]
<i>SLC25A47</i>	Hypermethylation	[217]
<i>SLC39A12</i>	Hypomethylation	[6]
<i>SMPD3</i>	Hypermethylation	[13]
<i>SFN</i>	Hypomethylation	[217]
<i>SGCA</i>	Hypomethylation	[6]
<i>TBX4</i>	Hypermethylation	
<i>TCAM1P-004</i>	Hypermethylation	[15]
<i>TKT</i>	Hypomethylation	[217]
<i>VTRNA2-1</i>	Hypermethylation	[221]
<i>ZBPB</i>	Hypermethylation	[6]

ACSL4: Acyl-CoA Synthetase Long Chain Family Member 4; *ALDH3A1*: Aldehyde Dehydrogenase 3 Family Member A1; *APOA5*: Apolipoprotein A5; *CLDN15*: Claudin-15; *CDKN2A*: cyclin-dependent kinase inhibitor 2A; *CYP7A1*: Cytochrome P450 Family 7 Subfamily A Member 1; *DEFB119*: Defensin β 119; *DPP6*: Dipeptidyl peptidase 6; *ENDOD1*: Endonuclease Domain Containing 1; *EZR*: Ezrin; *GLUL*: Glutamate-Ammonia Ligase; *GZMB*: Granzyme B; *MIR21*: microRNA-21; *Myo1g*: Myosin 1g; *NDRG2*: N-myc downstream-regulated gene family member 2; *NEFH*: Neurofilament, heavy polypeptide; *NKX3-2*: NK3 Homeobox 2; *PDE1A*: Phosphodiesterase 1A; *PHYHD1*: Phytanoyl-CoA Dioxygenase Domain Containing 1; *PRH2*: Proline-rich protein HaeIII subfamily 2; *RASSF1A*: Ras association domain family 1 isoform A; *SCAND3*: SCAN domain containing 3; *SFN*: Stratifin; *SGCA*: α -sarcoglycan; *SLC25A47*: Solute Carrier Family 25 Member 47; *SLC39A12*: Solute carrier family 39 member 12; *SMPD3*: sphingomyelin phosphodiesterase 3; *SPP1*: Secreted Phosphoprotein 1; *SPRR2A*: Small proline-rich protein 2A; *TBX4*: T-box 4; *TKT*: Transketolase; *VTRNA2-1*: Vault RNA 2-1; *ZBPB*: Zona pellucida binding protein.

events, given their downstream action on key promoters. By way of instance, *SET domain bifurcated histone lysine methyltransferase 1* (*SETDB1*), an H3K9-specific methyltransferase, has been reported to exhibit the most substantial increase in HCC in comparison to other epigenetic regulators [17]. *SETDB1* was shown to owe its overexpression in HCC to a gene duplication event, with an additional copy of chromosome 1q21 [17]. However, other anomalous events were discovered to contribute to its elevated levels, such as regulation by microRNAs (discussed below), or transcriptional activation such as this mediated by *specificity protein 1* (*SPI*) [17].

2.3. *DNMT3*. Contrary to *DNMT1*, *DNMT3a* and *DNMT3b* do not recognize hemimethylated DNA. They do not produce or maintain particular patterns of methylation [18], and they are not specifically associated with replication sites [19] as *DNMT1*. Rather, they mediate *de novo* methylation as mentioned previously. Additionally, it has been assumed that these DNMTs employ mechanisms different from *DNMT1* to access the heterochromatin [20], given the fact that they were found not to be associated with replication sites.

DNMT3 has been implicated in hepatocarcinogenesis. It has been expressly associated with hypermethylation of promoters controlling 22 tumor suppressor genes [21]. *DNMT3b* also exhibited a 4-fold increase of expression in HCC when compared to healthy livers, which correlated with poorer prognosis [21], which corroborates assumptions that *DNMT3* subtypes become overexpressed in cancer after having been downregulated postcellular differentiation [22].

In HCC of HBV etiology, the normally silenced *metastasis-associated protein 1* (*MTA1*) gene was upregulated by recruitment of *DNMT3a* and *DNMT3b* leading to hypomethylation of its promoter and increasing the tumor metastatic disposition [23]. Additionally, *DNMT3b* was elsewhere reported to be overexpressed by *telomerase reverse transcriptase* (*TERT*) in HCC. The resulting anomalous methylation patterns prompted activation of *AKT* [24]. Apart from its methylating capacity, *DNMT3b* was found to directly target *metastasis suppressor 1* (*MTSS1*), by direct binding to its promoter [25].

The implication of *DNMT3a* in HCC has also been corroborated. In a study by Zao et al., *DNMT3a* knockdowns displayed arrested cellular proliferation. Microarray analysis revealed concomitant upregulation of 153 genes, the preponderance of which bears CpG islands in their promoters. Among these activated genes was the tumor suppressor *PTEN* gene [26]. Moreover, *DNMTa* guided a conjectured distinction in the epigenetic dysregulation between different forms of liver cancer, where nonfibrolamellar HCC displayed significantly higher levels of *DNMTa* compared to the fibrolamellar variant [27]. This discrepancy was suggested to betray divergent epigenetic mechanisms in different HCC subtypes.

2.4. *DNMT3L*. Structurally similar and functionally complementary to *DNMT3a* and *DNMT3b* is *DNMT3L*, which, despite lacking intrinsic catalytic activity, enhances the binding of the former to S-adenosyl-L-methionine, the donor of

TABLE 2: DNA methyltransferase (DNMT) inhibitors in HCC. The table shows the most prominent DNMT inhibitors, the changes in the targets of the inhibited DNMTs, and the resulting effects on the tumor.

DNMT inhibitor	DNMT targets affected	Effect	Ref.
5-Azacytidine	<i>SLC10A1</i> , <i>CYP3A4</i> , <i>ALB</i> , and <i>miR-122</i>	Inhibits tumor growth	[29]
Decitabine	<i>p16INK4A</i> (activation)	G1 cell cycle arrest	[35]
	<i>PRSS3</i> (activation)	Inhibits proliferation and migration	[36]
Guadecitabine (SGI-110)	<i>DLEC1</i> , <i>RUNX3</i> , and <i>p16INK4A</i>	Inhibits tumor growth	[38]
Zebularine	<i>CDK2</i> , <i>Bcl-2</i> , and phosphorylation of <i>Rb</i> (inhibition) and <i>p21WAF/CIP1</i> and <i>p53</i> (activation)	Inhibits proliferation and induces apoptosis	[42]
SGI-1027	<i>Bcl-2</i> (inhibition) and <i>BAX</i> (activation)	Induces apoptosis	[222]
CM-272	<i>E-cadherin</i> , <i>CYP7A1</i> , <i>FBP1</i> , <i>GNMT</i> , and <i>MAT1A</i> (activation)	Inhibits proliferation and decreases adaptation to hypoxia	[223]
EGCG (Y6)	<i>P-gp</i> and <i>HIF1-α</i> (inhibition)	Inhibits proliferation and reverses doxorubicin-resistance	[53]
Genistein	<i>CYP1A1</i> , <i>CYP1B1</i> , and <i>p-AMPK</i> (activation) and <i>CYP26A1</i> and <i>CYP26B1</i> (inhibition)	Inhibits proliferation (at a 10-40 μM concentration) and induces apoptosis	[44]

ALB: albumin; *BAX*: Bcl-2-like protein 4; *Bcl-2*: B-cell lymphoma 2; *CDK2*: cyclin-dependent kinase 2; *CYP1A1*: cytochrome P450 1A1; *CYP1B1*: cytochrome P450 1B1; *CYP26A1*: cytochrome P450 26A1; *CYP26B1*: cytochrome P450 26B1; *CYP3A4*: cytochrome P450 3A4; *CYP7A1*: cholesterol 7α-hydroxylase-1; *DLEC1*: deleted in lung and esophageal cancer 1; *FBP1*: fructose-1,6-bisphosphatase; *GNMT*: glycine-N-methyl transferase; *HIF1-α*: hypoxia-inducible factor 1-α; *MAT1A*: methionine-adenosyltransferase 1A; *p16INK4A*: cyclin-dependent kinase inhibitor 2A; *p21WAF/CIP1*: cyclin-dependent kinase inhibitor 1; *p53*: tumor protein p53; *p-AMPK*: phosphorylated AMP-activated protein kinase; *P-gp*: P-glycoprotein 1; *Rb*: retinoblastoma; *RUNX3*: RUNX Family Transcription Factor 3; *SLC10A1*: sodium/bile acid cotransporter.

the methyl group. Understanding the role of *DNMT3L* in full requires further analysis [28].

Given all of the above, it is clear that modifying any of these anomalies could potentially serve as a therapeutic modality in HCC. Below the major DNMT inhibitors with reported activity in HCC are outlined.

2.5. DNMT Inhibitors. Herein, the most prominent inhibitors of DNMT in HCC are outlined. Despite the fact that—in many instances—DNMT inhibitors may not be selective for one subtype over the other, the following is reported according to what the original account relayed. DNMT inhibitors are summarized in Table 2.

2.6. 5-Azacytidine. 5-Azacytidine (5-AZA) is a synthetic analog of the nucleoside cytidine and an established inhibitor of *DNMT1*, marketed under the name Vidaza. In the context of HCC, treatment with 5-AZA conduced to tumor regression and a shift to a more differentiated phenotype, which was associated with regional demethylation of CpG regions upstream of the liver-specific genes *SLC10A1*, *CYP3A4*, *ALB*, and *miR-122*, which were downregulated pretreatments [29]. Additionally, this epigenetic modulation boosted the effects of sorafenib. 5-AZA triggered demethylation of 5-hydroxymethylcytosine (5hmC) via the *ten-eleven translocation proteins 2 and 3* [30]. *DNMT1* inhibition by 5-AZA was also found to synergize with immunotherapy via encouraging trafficking of T-cells to the tumor microenvironment secondary to a 5-AZA-induced upregulation of chemokine genes [31]. 5-AZA has been determined to be potentiated by sundry supplementation, such as vitamin C [32] and alendronate [33]. More recently, 5-aza-2'-deoxycytidine (5-Aza-CdR), a derivative of 5-AZA, was reported to downregulate *DNMT1*, *DNMT3a*, and *DNMT3b* [34].

2.7. Decitabine. Decitabine (5-aza-2'-deoxycytidine) is another analog of cytidine that also acts by blocking *DNMT1*. Decitabine was reported to demethylate the promoter of the *p16INK4A* gene, the product of which functions to regulate the cyclin-dependent kinases 4 and 6, leading to an upsurge of *p16INK4A* transcripts with ensuing G1 cell cycle arrest and a rise of the senescence-associated β-galactosidase [35]. Expression levels of *PRSS3* were also reported to rise in decitabine-treated cells [36]. The desilencing of *PRSS3* decelerated cellular proliferation due to inhibition of two cyclin/CDK complexes and downshifted migration through silencing *matrix metalloproteinase 2 (MMP2)*. A phase I/II clinical trial [37] scrutinized the efficacy of decitabine and its safety in advanced HCC. Western blots from patients' peripheral blood mononuclear cells (PBMCs) indicated decreased levels of *DNMT1* in decitabine-treated participants.

2.8. Guadecitabine. Guadecitabine is a dinucleotide derivative of decitabine in which the latter is attached to a deoxyguanosine is by a phosphodiester bridge. Guadecitabine is commonly designated as SGI-110 and exhibits a more sustained systemic effect than its parent compound. Demethylation and activation of the tumor suppressor genes *DLEC1*, *RUNX3*, and *CDKN2A* were observed following SGI-110 treatment of Huh7 and HepG2 cells. Although its demethylating effects were compromised in the presence of the histone H2A variant, macroH2A1, SGI-110 was still capable of restricting tumor growth, unlike decitabine [38]. Potentiation of the cytotoxicity of the platinum-based antineoplastic oxaliplatin was reported when a pretreatment of SGI-110 was coadministered [39]. The mechanistic basis of such a sensitization involves counteracting the extensive methylation of targets within the *Wnt/EGF/IGF* signaling loop.

2.9. Zebularine. In HepG2 cells cultured at high densities, zebularine, a more stable and less toxic analog of 5-AZA [40], demonstrated a progressive escalation of expression of differentiation-associated genes and fomented apoptosis. shRNA-induced *DNMT1* knockdown annulled these effects [41]. Paradoxically, contrary reports indicated that zebularine had negligible influence on DNA methylation in the same cell line [42]. Despite the previous report, zebularine did affect several cytotoxic events, which have been attributed to mechanisms other than DNMT inhibition. Zebularine was found to inhibit *histone deacetylases* (HDACs) alongside *DNMT* genes in LS 174T cells [43]. *DNMT1*, *DNMT3a*, and *DNMT3a* as well as Class I HDACs and Class II HDACs were downregulated with a concomitant elevation in the expression of *p21Cip1/Waf1/Sdi1*, *p27Kip1*, and *p57Kip2* on treatment with zebularine, albeit to a more modest extent in comparison with trichostatin A. In the same study, it was observed that both agents acted synergistically to substantially increase apoptosis. It would thus seem propitious to examine these regulatory loops more closely in HCC.

2.10. Genistein. Genistein (GE) is an isoflavone derived from soybean and is characterized by its propensity to bind the estrogen receptor. GE upregulated cytochromes *1A1* and *1B1* in HT29 cells and downregulated cytochromes *26A1* and *26B1* [44]. In Hep3B cells, GE increased levels of phospho-AMPK, which mitigated inflammatory processes and consequent liver damage [45]. In concert with trichostatin A (TSA), GE restored the expression of the DNA methyltransferases *DNMT1*, *DNMT3a*, and *DNMT3b* in HepG2 cells [46]. GE exhibited biphasic effects at different concentration ranges, where at a low concentration of 1 μ M, it encouraged cellular growth, while at higher concentration within the range of 10-40 μ M, GE had antiproliferative effects. Proapoptotic effects were evident at all concentrations, unlike TSA, whose effects were observable only following a 3-day long treatment [47].

2.11. Epigallocatechin-3-Gallate (EGCG). EGCG is the most abundant catechin in green tea that—among other flavonoids and catechins—has repeatedly been reported to possess tumor chemopreventive and antineoplastic effects in HCC [48]. EGCG has been shown to interact with the following amino acid residues within the catalytic domain of DNMT: P-1223, C-1225, S-1229, E-1265, and R-1309 [49, 50]. Moreover, catechol-containing polyphenols, of which EGCG is a member, inhibit DNMTs by mediating a rise in SAM O-methylation via catechol-O-methyltransferase. Alternatively, SAM levels were increased following disruption of the folate cycle secondary to dihydrofolate reductase inhibition by catechol-containing polyphenols. Direct inhibition of DNMTs by this class of compounds can also occur regardless of the methylation pattern [49, 50].

Additionally, EGCG has been shown to mediate a metabolic shift away from glycolysis in HCC cells, thereby promoting apoptosis and stunting cellular proliferation [51]. Mechanistically, this action has been attributed to its suppression of phosphofructokinase activity, whereby cellular stress is effected, ultimately culminating in programmed cell

death. What is more, EGCG synergistically acted to ameliorate the antiproliferative effects of sorafenib [51]. Synergy between EGCG and metformin, the famous antidiabetic biguanide, has also been reported [52]. An EGCG/metformin combination therapy was associated with a significant reduction in *glypican-3*, *survivin*, *cyclin D1*, *VEGF*, and the long noncoding RNA *AF085935* and an elevation of the levels of *caspase 3* [52]. Another study examined the therapeutic effects of Y6, a chemically modified form of EGCG [53]. Again, and similar to its parent compound, Y6 efficiently curbed cellular proliferation. Additionally, it engendered a reversal of doxorubicin resistance in resistant BEL-7404 cells. The antiproliferative and antiapoptotic effects of Y6 correlated with reduced *P-glycoprotein 1* (*P-gp*) and *HIF1- α* on the mRNA and protein levels and was exacerbated in groups receiving Y6/doxorubicin combination therapy, compared to those on doxorubicin monotherapy. A compendium of studies reporting disease-modifying capabilities of EGCG in HCC can be found in a recent review by Bimonte et al. [48].

Other inhibitors of DNMT such as hydralazine, procainamide, and RG108 have been tested for their efficacy in cancer [11] but are yet to be examined as potential therapies in HCC.

3. Histone Modifications

Chromatin is formed by the assembly of nucleosomal units, which are formed by the wounding of DNA around histone proteins. For accessing of genetic information, the highly packed chromatin has to be unwound. Chromatin modifications viz. methylation and acetylation are key controllers of this stipulation and thus play a crucial role in gene expression (Figure 1).

Histone modifications comprise sundry alterations to histone proteins including methylation (histone methyltransferases and histone demethylases), acetylation (histone acetyltransferases and histone deacetylases), ubiquitination, sumoylation, and phosphorylation [54]. The disruption of any of these modification patterns entails repercussions that may very well conduce to malignancy. However, for the purpose of this review, we elected to center this discourse on histone deacetylases (HDACs) given the abundance of data and the corroborated efficiency of HDAC inhibitors in preclinical and clinical settings [55]. Other reviews can be consulted for in-depth discussion of histone modifications and their implications in cancer [56–59].

Histone acetylation is controlled by two classes of enzymes: histone acetyltransferases (HATs) and histone deacetylases (HDACs). HATs catalyze the acetylation of lysine residues, whereas HDACs function to remove these acetyl groups [60].

As a result of acetylation, interaction between the histone octamers and DNA is compromised due to the neutralization of the positively charged lysine residues. The weakening of this interaction gives way to a transcriptionally permissive state of chromatin. HDACs promote an opposite effect, where the euchromatin state is favored as a consequence of retrieval of the positive charges on lysine residues, restoring the histone-DNA interaction [61]. A balance between HAT

FIGURE 1: Epigenetic modulation of chromatin by histone deacetylation and methylation/demethylation as well as DNA methylation. The figure highlights the role of histone deacetylases (HDACs), histone methyltransferase (HMTs), histone demethylases (HDMs), and DNA methyltransferases (DNMTs) in creating the epigenetic signature observed in HCC in addition to their significance as targets for therapy. As is shown, the most common site for such modifications occurs on specific lysine residues on histone H3. "Created with BioRender."

and HDAC activity ensures the maintenance of normal patterns of gene expression, and its disruption is often noted in many malignancies including HCC [62].

3.1. HDACs. There are around 18 HDACs, many of which have been shown to deacetylate nonhistone proteins [63]. Given the above, the centrality of HDACs to chromatin accessibility and control of gene expression [64] is obvious, and assumptions that HDACs constitute tumor suppressors or target for therapy are not only well-grounded but also experimentally evident.

In HCC, dysregulation of HDACs has been multiplied reported. By way of instance, *HDAC1* and *HDAC2* were found to be overexpressed in HCC patients of Southeast Asian origin and was associated with higher rates of mortality. Inhibition of these HDACs *in vitro* inhibited cellular proliferation [65]. The upregulation of *HDAC1* and *HDAC2* was found to suppress *fructose-1,6-bisphosphatase (FBP1)*, a key enzyme in glycolysis [66], and *HDAC2* was further reported to modulate genes involved in the cell cycle and apoptosis [67]. *HDAC3* was recently demonstrated to be centrally implicated in hepatocarcinogenesis. Following a ubiquitination event, it dissociates from the *c-Myc* promoter, whereby K9 of histone H3 (H3K9) becomes acetylated and *c-Myc* is made transcriptionally available [68]. Elimination of *HDAC3* inhibited the trimethylation of H3K9 that occurs subsequent to the *HDAC3*-mediated deacetylation of this residue, arrest-

ing the contingent double-strand break repair mechanism and resulting in the accretion of bad DNA [69].

Interestingly, HDACs were also shown to counter cell migration. Acetylation of H3K4 and H3K56 within the *Snail2* promoter was markedly reduced in EMT thanks to *HDAC1* and *HDAC3* [70]. It is worthy to note that G9a, a histone H3 lysine 9 (H3K9) methyltransferase, has been recently recognized as vital for such *Snail2*-mediated inhibition of *E-cadherin* and consequent repression of mesenchymal properties [71]. It has even been targeted for therapy by administering its inhibitor, UNC0646, in nanodiamonds, which reduced H3K9 methylation and tumor invasiveness [72].

That being said, therapeutic inhibition of HDACs may sometimes prove problematic because of interference with various pathways [56] and, as evident above, for the bidirectional functionality it has sometimes demonstrated. It is thus of essence to dedicate some efforts to better understand and characterize the complex regulatory role of HDACs so as to determine their amenability to therapeutic targeting and define in what direction should therapeutic strategies be pursued.

3.2. HDAC Inhibitors. HDAC inhibitors (HDACi) are a group of agents that are useful in resolving aberrant patterns of deacetylation, modulating chromatin accessibility, the lack of which is often an inciting factor for tumorigenesis [73]. Below the most prominent HDACis are outlined (Table 3).

TABLE 3: Histone deacetylase (HDAC) inhibitors in HCC. The table shows the most prominent HDAC inhibitors that have been studied in HCC, their cellular targets, and their antitumor effects.

HDACi	Target(s)	Hydroxamates	Effect	Ref.
Trichostatin A	<i>Apaf1</i> and <i>H2Aub</i> (activation)		Promotes apoptosis	[74]
	<i>ULBP1/2/3</i> and <i>MICA/B</i> (Activation)		Inhibits tumor cell growth	[77]
Resminostat	<i>Caspase 9</i> and <i>cytochrome c</i> (activation)		Promotes mitochondrial depolarization and apoptosis	[80]
Panobinostat	<i>Beclin1</i> , <i>Map1LC3B</i> , and <i>p53</i> (activation) and <i>p73</i> nuclear translocation		Promotes autophagy	[86]
Vorinostat (SAHA)	<i>HIF-α</i> (inhibition)		Initiating tumor hypoxia	[73]
	<i>DR5</i> (activation) and <i>c-Flip</i> (inhibition)		Sensitization to TRAIL-induced apoptosis	[224]
Quisinostat (±sorafenib)	<i>c-Caspase 3</i> , <i>c-Caspase 9</i> , <i>c-PARP</i> , and <i>Bax</i> (activation) and <i>Bcl-xL</i> , <i>Bcl-2</i> , <i>survivin</i> , <i>PI3K-p110</i> , <i>PI3K-p85</i> , and <i>p-AKT</i> (inhibition)		Inducing G0/G1 phase arrest and apoptosis	[225]
Cyclic peptides				
Romidepsin	<i>p-Erk</i> and <i>p-JNK</i> (activation)		Induces cell cycle arrest in the G2/M phase and apoptosis	[226]
Aliphatic fatty acids				
Valproic acid	<i>Nrf2</i> (inhibition)		Sensitization to proton irradiation	[94]
Valproic acid (+DOX)	<i>AKT/mTOR</i> (inhibition)		Increases ROS and induces autophagy	[95]
Sodium butyrate	<i>p-AKT</i> and <i>mTOR</i> (inhibition) and <i>CYLD</i> (activation)		Increases ROS and induces autophagy	[99], [76]

Bax: Bcl-2-associated X protein; *Bcl-2*: B-cell lymphoma 2; *Bcl-xL*: B-cell lymphoma extra large; *c-Caspase 3*: cleaved caspase 3; *c-Caspase 9*: cleaved caspase 9; *c-PARP*: cleaved Poly (ADP-ribose) polymerase; *CYLD*: CYLD lysine 63 deubiquitinase; *DOX*: doxorubicin; *DR5*: death receptor 5; *mTOR*: mammalian target of rapamycin; *Nrf2*: nuclear factor erythroid 2-related factor 2; *p-AKT*: phosphorylated protein kinase B; *p-Erk*: phosphorylated extracellular-signal-regulated kinase; *PI3K-p110*: phosphatidylinositol 3-kinase subunit p110; *PI3K-p85*: phosphatidylinositol 3-kinase subunit p85; *p-JNK*: phosphorylated c-Jun N-terminal kinase; *ROS*: reactive oxygen species.

4. Hydroxamates

4.1. Trichostatin A. TSA is one of the most studied hydroxamate HDAC inhibitors. Following inhibition of HDACs 1, 2, and 3 by TSA, *apoptotic protease-activating factor 1* (*Apaf1*) was determined to become upregulated, which leads to the stimulation of mitochondrial caspase-driven apoptosis of the HLE and HLF HCC cell lines [74]. TSA was also found to restore the expression level of *H2Aub*, an *H2A* posttranslationally ubiquitinated at lysine 119, which is diminished in HCC. Simultaneously, TSA modulated the rates of *H3S10* phosphorylation, which were inversely correlated with *H2Aub* in HCC [75]. In addition to *ubiquitin-specific peptidase 21* (*ups21*), which is responsible for the downregulation of *H2Aub* above, *CYLD* is another (lysine 63) deubiquitinase involved in the development of HCC. Contrary to *Ups21*, it is the inadequacy of *CYLD* that is associated with malignancy. TSA was shown to raise *CYLD* mRNA and protein levels in Huh7 and HepG2 cells [76]. Overexpression of ligands of *NKGD2* was noted following TSA treatment. It thus exerted its cytotoxic effect through stimulating natural killer (NK) cells to eliminate HCC cells [77]. Alternatively, the proapoptotic activity of TSA could be modulated by regulatory RNA species such as the long noncoding RNA, *lncRNA-uc002mbe.2*, which was increased post-TSA-treatment [78]. The proposed mechanism delineates an interaction between *lncRNA-uc002mbe.2* and *heterogeneous nuclear ribonucleoprotein A2B1* (*hnRNPA2B1*) which instigates the stimulation of *p21* and reduction of phosphorylated *AKT*. TSA has been used

in conjunction with other agents such as sorafenib for enhancing therapeutic outcomes [79].

4.2. Resminostat. Resminostat is a pan-HDACi (inhibits both nuclear and cytoplasmic HDACs). In HepG2, SMMC-7721 and HepB3 cells, resminostat incited mitochondrial depolarization and apoptosis via the mitochondrial permeability transition pore pathway. It also evoked the production of *caspase 9* and *cytochrome c* [80]. The cytotoxic effects of resminostat were reinforced by inhibitors of the *mammalian target of rapamycin* (*mTOR*), which has been characterized as a resistance factor of resminostat [81]. The synergistic effects of resminostat with sorafenib have been repeatedly studied. The combination proved safe and effective. Resminostat shifted the cells from a mesenchymal to an epithelial phenotype, which better sensitized the cells to subsequent sorafenib treatment [82]. That being said, further investigation into the advantage of this combination is required. While an exploratory clinical study corroborates the above observations [83], another phase I/II study refuted an added utility of resminostat supplementation over sorafenib monotherapy [84].

4.3. Panobinostat (PANB). Another potent pan-HDACi is PANB. Studies have shown that PANB affected a negative interference with DNMTs (as outlined in Table 2) and an ensuing impedence of methylation of classically hypermethylated genes, such as *APC* and *RASSF1A* [85]. PANB encouraged an increase of autophagic factors *Beclin1* and

Map1LC3B, which concomitantly presented with the appearance of quasiautophagosome clusters along with the nuclear translocation of *p53* and *p73* in HepG2 and Hep3B cells, respectively, and regulation of *DRAM1* [86]. Ingeniously, ^{18}F probes have been used as PET tracers to monitor angiogenic progression following PANB therapy, through imaging of integrin $\alpha v\beta 3$. These PET scans revealed a substantially reduced uptake in HepG2 but not in HT29 neoplasm, in response to therapy in nude mice [87].

4.4. Vorinostat (VORN; SAHA). Beyond chromatin unwinding, evidences have been provided that substantiate a role of VORN in initiating tumor hypoxia. Ostensibly, VORN-mediated acetylation of *heat shock protein 90* (*Hsp90*), a chaperone of *HIF- α* , hinders its nuclear translocation and forestalls its transcriptional activity [73]. As a result, levels of several downstream hypoxia-triggered molecules come to be deficient. VORN was used as an adjuvant to a number of anticancer drugs such as oxaliplatin [88] and the *mTOR* inhibitor, sirolimus [89]. Compared to 5-aza-2'-deoxycytidine (5-Aza-CdR), VORN exhibited superior apoptotic effects which was coincident with its inhibition of *HDAC1*. However, a combination of the two achieved maximal apoptosis of LCL-PI 11 cells [34].

4.5. Belinostat. Belinostat has been studied extensively but sporadically in different cancer types, mostly on hematologic malignancies. Despite its consistently promising results, belinostat remains underinvestigated in HCC. Hereunder, most of the reports on belinostat use in HCC are summarized. A multicenter phase I/II study aimed at determining the drug pharmacokinetic and toxicity profiles constitutes one major such report. The outcomes of the study were favorable in terms of disease stabilization (assessed via histoscores) and high tolerance to the drug, which is reflected in its outspread pharmaceutical window [78]. When combined with the checkpoint inhibitors anti-*PD-1* and anti-*CTLA-4* antibodies, belinostat potentiated the latter but not the former. The synergy was credited to a drop of regulatory T cells and a boosted *IFN- γ* production by T cells in the tumor microenvironment [90]. Withal, *PD-L1* inhibition was proposed, given its observed overexpression on antigen-presenting cancer cells and its retarded expression on effector T cells. Boron-incorporating prodrugs of belinostat have been propounded for improving its potency against solid tumors [91]. The pro-drug form manifested superior bioavailability. However, the efficacy of this form remains to be examined in HCC.

5. Aliphatic Fatty Acids

5.1. Valproic Acid (VPA). VPA, a class I and IIa HDACi, has a certain favorability to it, given its reasonable cost and wide safety margin. VPA demonstrated antineoplastic effects in PLC/PRF5 and HepG2 cells [92]. Moreover, VPA was shown to mediate a dissemination of its anticancer activity through its indirect modulation of cell-free DNA. This rather unique study was conducted under the hypothesis that cfDNA can mediate intercellular signaling. The cfDNA derived from VPA-treated cells induced glycolysis in naïve HepG2 cells.

Subsequent analysis of the cfDNA from these cells revealed altered characteristics. As such, it was suggested that VPA treatment can be temporarily propagated across cells via their released cfDNA [93]. VPA rendered Hep3B cells more vulnerable to proton irradiation, protracting the actuated DNA damage, and promoted irradiation-mediated apoptosis [94]. Curiously, VPA increased irradiation-induced reactive oxygen species (ROS) production and silenced *nuclear factor erythroid 2-related factor 2* (*Nrf2*), which is quickly becoming a marker of radioresistance. VPA has been used in combination with doxorubicin [95] and sorafenib [96] and boosted the cytotoxic effects of cytokine-induced killer cells [97]. Recently, VPA was assessed alongside zebularine as to the effect on *Suppressor of cytokine signaling 1* (*SOCS-1*) and *Suppressor of cytokine signaling 3* (*SOCS-3*) expression [98]. Despite both suppressing cellular growth, only VPA demonstrated an apoptotic effect and correlated with an upregulation of *SOCS-1* and *SOCS-3*.

5.2. Sodium Butyrate. Butyrate is among the short chain fatty acids that are produced as a result of the anaerobic fermentation undergone by gut microbiota, and its benefits in restraining tumor growth have been documented. The sodium salt of butyrate has been explored as an epigenetic modulator in various malignancies. However, there remains a need for exploring its utility in HCC. Elevation of ROS and consequent autophagy were noted in Huh7 cells following butyrate treatment. Levels of phosphorylated *AKT* and *mTOR* were positively inhibited, which gave to a dependent rise in *ATG5*, *Beclin1*, and *LC3-II*, with subsequent assembly of the autophagosome machinery [99]. Otherwise, as noted with TSA (above), butyrate spurred on the expression of the deubiquitinase *CYLD* in Huh7 and HepG2 cells (Kotantaki & Mosialos, 2016).

6. Noncoding RNAs

6.1. MicroRNAs. MicroRNAs (miRNAs) are probably the most frequently studied biomolecules in cancer, and for a good reason. Given their integral role in gene expression manipulation, abnormal miRNome lies at the heart of the genetic dysregulation that predisposes to oncogenesis. miRNAs are encoded mostly in intergenic regions of the genome and are transcribed by RNA polymerase II. Following transcription, a primary RNA transcript forms a hairpin loop with terminal single-stranded extensions (Figure 2). Both the 5' and 3' extensions are cleaved off by a microprocessing complex made up of *DROSHA*, a class 2 RNase III and its accessory protein *DGCR8*, yielding what is referred to as a precursor miRNA (pre-miRNA) (Figure 2). The pre-miRNA is exported to the cytoplasm shuttled through nuclear pores by the transporter *exportin 5* (Figure 2). In the cytoplasm, the pre-miRNA is recognized by the *TRPB2*-bound enzyme *Dicer*, another RNase III, which clips off the loop, producing a double-stranded miRNA (ds-miRNA or miR/miR* duplex) (Figure 2). The Argonaute protein, *Ago2*, interacts with *Dicer* to bind the ds-miRNA, unwinding the miRNA duplex, releasing the passenger strand that is degraded and retains the guide strand (Figure 2), which is

FIGURE 2: A schematic showing a network of several miRNAs with converging regulatory pathways in HCC therapy. The figure shows miRNAs sharing a common target as well as targets regulated by more than one miRNA. The therapeutic effects associated with all of the microRNAs in the illustrated panel correlate with their upregulation, except for miR-101 (marked). “Created with BioRender.”

15-25 nucleotides long [100, 101]. Along with Ago2, the guide strand interacts with a group of proteins forming the *RNA-induced silencing complex (RISC)* which constitutes the active silencing species. Complementarity with the 3' UTR of target mRNAs determines which are marked for silencing, which is further reinforced by near-perfect complementarity of the mRNA with the miRNA seed sequence. The bound mRNA may be degraded or its translation impeded, turning off the mRNA-encoding gene. Hereinafter, some of the most therapeutically bioactive miRNAs are explored.

6.2. miR-126. miR-126 was shown to target *EGFL7* and *VEGF* in HCC tissues, lowering their expression [102]. Gain of function studies demonstrated that this regulatory mechanism resulted in significant reduction of tumor size and weight as well as a decreased microvascular density of transplanted neoplasms. Other studies further corroborated the antiangiogenic role of miR-126. miR-126-transfected HepG2 cells were transplanted in nude mice in parallel with a control group receiving a transplant of nontransfected cells. Postresection analysis revealed lower VEGF expression levels in the miR-126 group compared with controls as well as rela-

tively reduced tumor volumes [103]. Du and colleagues [104] reported similar findings for the 3p arm of miR-126. According to the results of their experiments, miR-126-3p gain of function inhibited expansion of tumor vasculature and reduced microvascular density and capillary tube formation. *Low-density lipoprotein receptor-related protein 6 (LRP6)* and *phosphoinositide-3-kinase regulatory subunit 2 (PIK3R2)* were identified as the direct targets, and their silencing occasioned similar effects to those brought about by overexpression of miR-126-3p. Beyond its effects on tumor vascularization, miR-126 has manifested antiproliferative and antiapoptotic functionalities. Zhao et al. [105] reported *sex-determining region Y-box 2 (SOX2)* as a putative target of miR-126. miR-126 mimics correlated with downregulated levels of SOX2 and subsequent cell cycle arrest and apoptosis in HepG2 cells. In addition to the above, miR-126 repressed metastatic capability of HCC. A negative correlation between miR-126 and *ADAM metalloproteinase domain 9 (ADAM9)* has been established in hepatitis B virus-related HCC [106]. Upregulation of miR-126 attenuated ADAM9 expression and consequently inhibited tumor migration and reduced instances of metastases. Ectopic expression of miR-126 was

associated with failure of *miR-126*-transfected SMMC-7721 cells to achieve pulmonary colonization *in vivo* [107]. The *miR-126-3p/PIK3R2/LRP6* regulatory loop mentioned above has also been proven to result in the suppression of cellular migration, ECM invasion, and tumor metastasis [104].

6.3. *miR-148a*. *miR-148a* has recently been shown to post-transcriptionally regulate the expression of *transferrin receptor 1 (TFR1)* [108]. Given the negative correlation observed, an increase in *miR-148a* levels is surmised to downregulate *TLR1* in HCC, resulting in reduced uptake of transferrin-bound iron by the cancer cells, which consequently leads to a drop in cellular iron levels, suppressing proliferation. The closely related *miR-148b* is purported to directly target *Rho-associated protein kinase 1 (ROCK1)* to similar antiproliferative effects [109]. Other endeavors indicated that *miR-148a* mimics might be implicated in the regulation of hepatocytic differentiation via regulating the *IKK α /NUMB/NOTCH* pathway [110]. Furthermore, *miR-148a* positively correlated with the expression of *E-cadherin* and downregulated mesenchymal markers, i.e., *vimentin*, *fibronectin*, and *N-cadherin* in hepatoma cells, by binding and inhibiting *Met* and attenuating its downstream signaling, ultimately resulting in decreased nuclear accumulation of *SNAIL* [111]. As such, *miR-148a* was effective in discouraging EMT and suppressing pulmonary metastasis. A number of studies sought to examine the role of microRNAs in regulating hepatic stellate cells (HSCs), to outstanding outcomes. *miR-148a* was shown to target and inhibit *growth arrest-specific gene 1 (Gas1)* mRNAs, thwarting Hedgehog signaling and preventing biogenesis of autophagosomes, which manifested as enhanced autophagy and apoptosis of HSCs [112]. Interestingly, *miR-148a* itself has been shown to be epigenetically regulated in HCC. By virtue of its hypermethylated CpG island, *miR-148a* is typically silenced in HCC cell lines [113]. Ironically, *DNMT1*, an established target of *miR-148a*, is the DNA methyltransferase that mediates such hypermethylation. *DNMT1* is upregulated in HCC, and thus, it downplays its primary regulator by a negative feedback loop. Fortunately, ectopic expression of *miR-148a* abrogates the inhibitory effects of *DNMT1*, permitting its regulatory role to take effect.

6.4. *miR-199a*. *miR-199a-3p* prompted a diminution of malignant nodular size and numbers in a transgenic mouse model that is prone to developing HCC, coinciding with a downregulation of its putative targets: *p21 activated kinase 4 (PAK4)* and *mTOR*, and hence a drop in the levels of *FOXO1*, replicating effects observed following treatment with sorafenib [114]. Targeted delivery of *miR-199a-3p* to neoplasms in nude mice displayed similar auspicious outcomes. Mimics of the 3p arm of *miR-199a* were encapsulated in bionic acid- (BA-) functionalized peptide-based nanoparticles (NPs). Hepatospecific delivery was achieved through the high affinity interaction between BA and the asialoglycoprotein receptors, which are overexpressed in HCC cells. Mirroring *mTOR* inhibition *in vitro*, apoptotic and antiproliferative events were noted, following IV administration of the NPs [115]. Preceding *in vitro* analysis had additionally exposed an upregulation of *PUMA* secondary to a rise in

ZHX1 levels, concurring with repressed growth. Increased cell death was paralleled by *Bcl2* tapering off and accretion of *cleaved caspase 3* and *Bax* [116]. Both arms of *miR-199a* positively modulated *E-cadherin* through inhibition of its *Notch1*-mediated suppression [117], which also suggests a role for *miR-199a* in checking EMT. *miR-199a-5p* was also shown to restrain metastatic disposition by silencing *Snail1* [118]. The biotherapeutic activity of the 5p arm extends well beyond its regulation of *E-cadherin*. Upwards of EMT, introducing *miR-199a-5p* stifled *clathrin heavy chain (CTLC)* expression arresting cellular growth *in vitro* and xenograft mice models [119]. Moreover, *VEGF*-initiated cell proliferation was reportedly halted posttreatment with *miR-199a-5p*, thanks to its modulation of the *nitroreductase, NOR1* [120].

6.5. *miR-503*. Several studies reported antimetastatic effects of *miR-503* through dampening the expression of various targets such as *WEE1* [121], *PRMT1* [122], and *ARHGEF19* [123]. Decelerated cellular growth, inducement of apoptosis, and sensitization to chemotherapy were all events associated with *miR-503* gain of function and were collateral to its modulation of its determined targets viz. *eukaryotic translation initiation factor 4E (EIF4E)* [124] and *insulin-like growth factor 1 receptor (IGF-1R)* [125].

6.6. *miR-101*. *miR-101* has been a confirmed tumor suppressor and recurrently reported as a downregulated species in HCC. Marked clampdown of tumor growth has been linked to the modulation of the *HGF/c-MET* axis by *miR-101-3p* [126]. *miR-101* also attenuated the expression of the *zinc-finger protein 217 (ZNF217)*, a potent effector of malignant immortalization [127]. Further, vasculogenic mimicry, an insidious mechanism of *de novo* vasculogenesis by which cancer resists angiogenic arrest, was undermined by *miR-101* mimics, which sabotaged *TGF- β* and *SDF1* signaling in cancer-associated fibroblasts and impaired *VE-cadherin* expression [128]. Similar to *miR-503*, *miR-101-3p* also targeted *WEE1*, which was shown to sensitize Huh7 and PLC5 to radiotherapy, an effect that is partially abrogated in HCC by the lncRNA *nuclear-enriched abundant transcripts 1 and 2 (NEAT1 and NEAT2)* [129]. On top of that, *miR-101* subverted the *TGF- β 1*-instigated build-up of extracellular matrix (ECM), reversing hepatic fibrosis, and blunted the levels of phosphorylated *PI3K*, *mTOR*, and *Akt* [130]. As with other epigenetic modulators, *miR-101* has been tried as a part of several combinatorial regimens. Synergy was reported with liposomal doxorubicin [131] and the lncRNA *LINC00052*, which promoted the expression of the 3p arm of *miR-101* that restricted the expression of *SRY-related HMG-box gene 9 (SOX9)* [132].

As is evident in Figure 2 and Table 4, different miRNAs have common targets and inevitably a single target can be regulated by more than one miRNA, which creates an elaborate regulatory network and sometimes complicate the utilization of miRNAs for diagnostic and therapeutic purposes.

6.7. Long Noncoding RNAs. Another major class of nonprotein-coding RNAs that is central to HCC and which is gaining significant attention as of late is long noncoding RNAs

TABLE 4: MicroRNAs (miRNAs) with disease-modifying effects in HCC. The table shows the direction of microRNA expression associated with the therapeutic effects, the regulated targets, and the observed effects in HCC.

MicroRNA	Expression changes associated with therapeutic effects	Effect	Targets (and the direction of their therapeutic regulation)	Reference
<i>let-7c</i>	Upregulation	Induction of apoptosis and inhibition of proliferation	<i>LIN28B</i> , <i>ARID3B</i> , <i>Bcl-xL</i> , and <i>c-Myc</i> (downregulation)	[227]
<i>miR-663b</i>	Upregulation	Suppression of tumor proliferation and invasiveness	<i>GAB2</i> (downregulation)	[228]
<i>miR26a</i>	Upregulation	Growth inhibition, migration, invasion, colony formation; initiation of hepatoselective apoptosis. Enhancement of chemosensitivity	<i>CCND2</i> , <i>IL-6</i> , and <i>PIK3C2α</i> (downregulation)	[229, 230]
<i>miR-122</i>	Upregulation		<i>ADAM17</i> , <i>CCNG1</i> , <i>ADAM10</i> , and <i>Bcl-w</i> (downregulation)	
<i>miR-621</i>	Upregulation	Amelioration of tumor radiosensitivity	<i>SETDB1</i> (downregulation)	[231]
<i>miR-299-5p</i>	Downregulation	Suppression of proliferation, migration, and invasion; initiation of apoptosis	<i>SLAH1</i> (upregulation)	[232]
<i>miR-577</i>	Upregulation	Inhibition of EMT and metastasis	<i>HOXA1</i> (downregulation)	[233]
<i>miR-501-3p</i>	Upregulation	Inhibition of proliferation, EMT, migration, and invasion	<i>LIN7A</i> (Downregulation)	[234]
<i>miR-378a</i>	Upregulation	Inhibition of proliferation and enhancement of sensitivity to sorafenib-based chemotherapies	<i>VEGFR₂</i> , <i>PDGFRβ</i> , <i>MMP-2</i> , and <i>c-Raf</i> (downregulation)	[235]
<i>miR-204-5p</i>	Upregulation	Inhibition of cellular proliferation and clonogenicity	<i>SIX1</i> (downregulation)	[236]
<i>miR-495</i>	Upregulation	Inhibition of proliferation and invasion	<i>IGFIR</i> (downregulation)	[237]
<i>miR-758-3p</i>	Upregulation	Inhibition of proliferation, migration, and invasion	<i>MDM2</i> and <i>mTOR</i> (downregulation)	[238]
<i>miR-30a-5p</i>	Upregulation	Inhibition of proliferation and invasion	<i>FOXA1</i> (downregulation)	[239]
<i>miR-196a</i>	Downregulation	Induction of apoptosis	<i>FOXO1</i> (upregulation)	[240]
<i>miR-30a</i>	Upregulation	Induction of apoptosis	<i>KRAS</i> (downregulation)	[241]
<i>miR-326</i>	Upregulation	Induction of apoptosis and inhibition of proliferation and invasion	<i>LASPI</i> (downregulation)	[242]
<i>miR-708</i>	Upregulation	Inhibition of proliferation, migration, and invasion	<i>SMAD3</i> (downregulation)	[243]
<i>miR-296-5p</i>	Upregulation	Inhibition of proliferation, migration, and invasion	<i>AKT2</i> (downregulation)	[244]
<i>miR-24-1</i>	Upregulation	Downregulation of c-Myc at the protein level and suppression of its O-GlcNAcylation; reduction of metastatic potential	<i>OGT</i> (downregulation)	[245]
<i>miR-203a-3p</i>				
<i>miR-548aa</i>				
<i>miR-376b-3p</i>	Upregulation	Inhibition of proliferation	<i>GPC3</i> (downregulation)	[246]
<i>miR-548v</i>				
<i>miR-4510</i>				
<i>miR-211-5p</i>	Upregulation	Inhibition of proliferation and apoptosis; enhancement of drug sensitivity	<i>ZEB2</i> (downregulation)	[247]
<i>miR-138</i>	Upregulation	Promotion of TRAIL-induced apoptosis	<i>ISG15</i> (downregulation)	[248]
<i>miR-592</i>	Upregulation	Inhibition of proliferation, migration, and invasion	<i>IGF-1R</i> (downregulation)	[249]
<i>miR-365</i>	Upregulation	Initiation of apoptosis	<i>Bcl-2</i> (downregulation)	[250]

TABLE 4: Continued.

MicroRNA	Expression changes associated with therapeutic effects	Effect	Targets (and the direction of their therapeutic regulation)	Reference
<i>miR-217</i>	Upregulation	Suppression of proliferation, migration, and invasion; initiation apoptosis	<i>MTDH</i> (downregulation)	[251]
<i>miR-199a-5p</i>	Upregulation	Decreased cell viability and colony formation; cell cycle arrest	<i>CLTC</i> (downregulation)	[119]
<i>miR-185</i>	Upregulation	Inhibition of proliferation; G0/G1 arrest; promotion of apoptosis	<i>RHEB</i> , <i>RICTOR</i> , and <i>AKT1</i> (downregulation)	[252]
<i>miR-503</i>	Upregulation	Repression of proliferation and sensitization to anticancer drugs	<i>EIF4E</i> (downregulation)	[124]
<i>miR-377</i>	Upregulation	Inhibition of invasion and migration; repression of EMT	<i>PRMT1</i> (downregulation)	[122]
<i>miR-199a-3p</i>	Upregulation	Suppression of proliferation and induction of apoptosis	<i>Bcl-xL</i> (downregulation)	[253]
<i>miR-22</i>	Upregulation	Growth inhibition and induction of apoptosis	<i>ZHX1</i> and <i>PUMA</i> (upregulation) and <i>Bcl-2</i> (downregulation)	[166]
	Downregulation	Inhibition of proliferation, migration, and invasion	<i>CD147</i> (downregulation)	[254]
<i>miR-101</i>	Upregulation	Repression of TGF- β and CD206 in M2 cells; inhibition of macrophage-driven HCC	<i>DUSP1</i> (upregulation)	[255]
		Suppression of proliferation, colony formation, EMT, and angiogenesis as well as VM. Inhibition of intrahepatic and distant metastases. Synergized with doxorubicin or fluorouracil to induce apoptosis	<i>TGF-βR1</i> , <i>Smad2</i> , <i>SDF1</i> , <i>VE-cadherin</i> , <i>EZH2</i> , <i>COX2</i> , <i>STMN1</i> , and <i>ROCK2</i> (downregulation)	[128, 256, 257]
<i>miR-3178</i>	Upregulation	Inhibition of proliferation, G1 arrest, and promotion of apoptosis	<i>EGR3</i> (downregulation)	[258]
<i>LNA-antimiR-214</i>	Upregulation	Reduction in fibrosis	<i>miR-214</i> (downregulation)	[259]
<i>miR-190a</i>	Upregulation	Suppression of migration and invasion	<i>treRNA</i> (downregulation)	[260]
<i>miR-491</i>	Upregulation	Lowering of cancer stem cell-like properties; inhibition of extracellular signal-regulated kinases	<i>GIT-1</i> (downregulation)	[261]
<i>miR-497</i>	Upregulation	Inhibition of colony formation and tumor growth	<i>IGF-1R</i> (downregulation)	[262]
<i>miR-663</i>	Downregulation	Inhibition of proliferation and promotion of apoptosis	<i>TGFβ1</i> (upregulation)	[263]
<i>miR-20a</i>	Upregulation	Promotion of apoptosis; inhibition of proliferation, invasion, and migration	<i>CCND1</i> (downregulation)	[264]
<i>miR-148a</i>	Upregulation	Suppression of tumor growth and malignancy. Promotion of differentiated phenotype	<i>IKKα</i> (downregulation)	[110]
<i>miR-381</i>	Upregulation	Inhibition of proliferation, colony formation, invasion, and induction of G0/G1 arrest	<i>LRH-1</i> (downregulation)	[265]
<i>miR-27a-3p</i>	Upregulation	Inhibition of EMT, metastasis, and VM	<i>VE-cadherin</i> (downregulation)	[266]
<i>miR-26b-5p</i>	Upregulation	Suppression of Twist1-induced EMT	<i>SMAD1</i> (downregulation)	[267]
<i>miR-30a-5p</i>	Upregulation	Inhibition of proliferation, colony formation, and induction of apoptosis	<i>MTDH</i> (downregulation)	[268]
<i>miR-33a-3p</i>	Upregulation	Suppression of cellular growth and migration/invasion	<i>PBX3</i> (downregulation)	[269]
<i>miR-145</i>	Upregulation	Inhibition of activation and proliferation of hepatic stellate cells	<i>ZEB2</i> (downregulation)	[270]
<i>miR-1258</i>	Upregulation	Inhibition of proliferation, G0/G1 arrest, and induction of apoptosis	<i>CKS1B</i> (downregulation)	[271]

TABLE 4: Continued.

MicroRNA	Expression changes associated with therapeutic effects	Effect	Targets (and the direction of their therapeutic regulation)	Reference
<i>miR-1299</i>	Upregulation	G0/G1 arrest and inhibition of proliferation	<i>CDK6</i> (downregulation)	[272]
<i>miR-200a</i>	Upregulation	Inhibition of EMT and decreased mitochondrial metabolism	<i>CXCL1</i> (downregulation)	[273]
<i>miR-486-5p</i>	Upregulation	Repression of proliferation, cellular viability, migration, and clonogenicity	<i>IGF-1R</i> , <i>mTOR</i> , <i>STAT3</i> , and <i>c-Myc</i> (downregulation)	[274]
<i>miR-199a-5p</i>	Upregulation	Inhibition of proliferation, migration/invasion, and synergized with chemotherapeutics	<i>E2F3</i> (downregulation)	[275]
<i>miR-1285-3p</i>	Upregulation	Inhibition of proliferation	<i>JUN</i> (downregulation)	[276]
<i>miR-449a</i>	Upregulation	Inhibition of motility and pulmonary metastasis; increase of epithelial markers and reduction of mesenchymal markers; reduction of Snail nuclear accumulation	<i>FOS</i> and <i>Met</i> (downregulation)	[277]
<i>miR-302b</i>	Upregulation	Sensitization to 5-FU	<i>MCL-1</i> and <i>DPYD</i> (downregulation)	[278]
<i>miR-143</i>	Downregulation	Inhibition of proliferation due to a G0/G1 arrest; induction of apoptosis	<i>TLR2</i> , <i>NF-κB</i> , <i>MMP-2</i> , <i>MMP-9</i> , <i>CD44</i> , <i>MMP14</i> , <i>integrin β1</i> , and <i>integrin β4</i> (downregulation)	[279]
<i>miR-324-5p</i>	Upregulation	Subduing invasiveness and metastatic capacity; downregulation of MMP2 and MMP9	<i>ETS1</i> and <i>SP1</i> (downregulation)	[279]
<i>miR-26b</i>	Upregulation	Inhibition of proliferation, invasion, and migration	<i>EphA2</i> (downregulation)	[280]
<i>miR-449</i>	Upregulation	Suppression of DNA replication, mitotic entry, and cellular proliferation	<i>SIRT1</i> and <i>SREBP-1c</i> (downregulation)	[281]
<i>miR-221</i>	Downregulation	Lowering of proliferation and clonogenicity; inhibition of migration/invasion; induction of G1 arrest and apoptosis	<i>BMF</i> , <i>BBC3</i> , and <i>ANGPTL2</i> (downregulation)	[282]
<i>miR-206</i>	Upregulation	Cell cycle arrest and inhibition of proliferation, invasion, and migration. Induction of apoptosis	<i>Notch3</i> , <i>HES1</i> , <i>Bcl-2</i> , and <i>MMP-9</i> (downregulation) and <i>p57</i> , <i>Bax</i> , and <i>cleaved caspase 3</i> (upregulation)	[283, 284]
<i>miR-148a</i>	Upregulation	Repression of EMT and pulmonary metastasis; increase of epithelial markers; reduction of mesenchymal markers	<i>Met</i> (downregulation)	[111]
<i>miR-152</i>	Upregulation	Inhibition of proliferation, cellular motility, and promotion of apoptosis	<i>TNFRF6B</i> (downregulation)	[285]
<i>miR-99a</i>	Upregulation	Inhibition of proliferation	<i>Ago2</i> (downregulation)	[286]
Anti- <i>miR-197</i>	Upregulation	Inhibition of migration and invasion; upregulation of CD82	<i>miR-197</i> (downregulation)	[287]
<i>miR-26b</i>	Upregulation	Sensitization of cells to doxorubicin-induced apoptosis	<i>TAK1</i> and <i>TAB3</i> (downregulation)	[288]
<i>let-7a</i>	Upregulation	Inhibition of local invasion and migration	<i>KRAS</i> , <i>HRAS</i> , and <i>NRAS</i> (downregulation)	[289]
<i>miR-126-3p</i>	Upregulation	Inhibition of migration and invasion; suppression of capillary tube formation; reduction of tumor volume and microvessel density	<i>LRP6</i> and <i>PIK3R2</i> (downregulation)	[104]
<i>miR-302c</i>	Upregulation	Attenuation of HUVECs motility; upregulation of VE-cadherin; downregulation of β-catenin, FSP1, and α-SMA; growth inhibition in cocultures	<i>MTDH</i> (downregulation)	[290]

TABLE 4: Continued.

MicroRNA	Expression changes associated with therapeutic effects	Effect	Targets (and the direction of their therapeutic regulation)	Reference
<i>miR-148b</i>	Upregulation	Inhibition of proliferation, metastasis and angiogenesis. Improvement of chemosensitivity	<i>NRP1</i> (downregulation)	[291]
<i>miR-1188</i>	Upregulation	Inhibition of proliferation, migration, invasion, and promotion of apoptosis	<i>Bcl-2</i> and <i>Sp1</i> (downregulation)	[292]
<i>miR-126</i>	Upregulation	Inhibition of proliferation, cell cycle arrest, and induction of apoptosis	<i>SOX2</i> (downregulation)	[105]
<p><i>ADAM10</i>: ADAM metalloproteinase domain 10; <i>ADAM17</i>: ADAM metalloproteinase domain 17; <i>Agg2</i>: Argonaute 2; <i>AKT1</i>: AKT serine/threonine kinase 1; <i>AKT2</i>: AKT serine/threonine kinase 2; <i>ANGPTL2</i>: Angiotensin-like 2; <i>ARID3B</i>: AT-rich interaction domain 3B; <i>BAD</i>: Bcl-2-associated agonist of cell death; <i>BAX</i>: Bcl-2-associated X; <i>BBC3</i>: Bcl-2 binding component 3; <i>Bcl-2</i>: B-cell lymphoma 2 apoptosis regulator; <i>Bcl-w</i>: Bcl-2-like protein 2; <i>Bcl-xL</i>: B-cell lymphoma extra large; <i>BMF</i>: Bcl-2 modifying factor; <i>CCND1</i>: Cyclin D1; <i>CCND2</i>: Cyclin D2; <i>CCNG1</i>: Cyclin G1; <i>CD133</i>: CD133 antigen (prominin-1); <i>CD147</i>: Cluster of differentiation 147 (Basigin); <i>CDK6</i>: cyclin-dependent kinase 6; <i>CKS1B</i>: CDC28 protein kinase regulatory subunit 1B; <i>CLTC</i>: clathrin heavy chain; <i>c-Myc</i>: Myc protooncogene; <i>BHLH</i> transcription factor; <i>COX2</i>: cytochrome C oxidase subunit II; <i>c-Raf</i>: Raf-1 protooncogene, serine/threonine kinase; <i>CXCL1</i>: C-X-C motif chemokine ligand 1; <i>DPYD</i>: Dihydropyrimidine dehydrogenase; <i>DUSP1</i>: Dual specificity phosphatase 1; <i>E2F3</i>: E2F transcription factor 3; <i>EGR3</i>: EGR3 early growth response 3; <i>EIF4E</i>: eukaryotic translation initiation factor 4E; <i>EphA2</i>: Ephrin receptor A2; <i>ETS1</i>: ETS protooncogene 1; <i>EZH2</i>: enhancer of zeste 2 polycomb repressive complex 2 subunit; <i>FOX</i>: Fos protooncogene, AP-1 transcription factor subunit; <i>FOXO1</i>: Forkhead box O1; <i>FOXO1</i>: Forkhead box O1; <i>GAB2</i>: GRB2-associated-binding protein 2; <i>GIT-1</i>: GIT ArfGAP 1; <i>GIPC3</i>: Glypican 3; <i>HES1</i>: Hair cell enhancer of split-1; <i>HOXA1</i>: Homeobox A1; <i>IGFIR</i>: insulin-like growth factor 1 receptor; <i>IKKα</i>: Inhibitor of κB kinase α; <i>IL-6</i>: interleukin-6; <i>ISG15</i>: interferon-stimulated gene 15; <i>JUN</i>: Jun protooncogene; AP-1 transcription factor subunit; <i>LASPI</i>: LIM and SH3 protein 1; <i>LIN28B</i>: Lin-28 homolog B; <i>LIN28A</i>: Lin-7 homolog A, crumbs cell polarity complex component; <i>LRRH-1</i>: liver receptor homolog-1; <i>LRP6</i>: low-density lipoprotein receptor-related protein 6; <i>MCL-1</i>: MCL1 apoptosis regulator; <i>MDM2</i>: MDM2 protooncogene; <i>MET</i>: MET protooncogene, receptor tyrosine kinase; <i>MMP-2</i>: matrix metalloproteinase-2; <i>MMP-9</i>: matrix metalloproteinase-9, p57; <i>MTDH</i>: metadherin; <i>mTOR</i>: mammalian target of rapamycin; <i>NRP1</i>: Neuropilin-1; <i>OGT</i>: O-GlcNAc transferase; <i>OTUD7B</i>: OTU deubiquitinase 7B; <i>PBX3</i>: Pre-B-cell leukemia homeobox 3; <i>PDGFRβ</i>: Platelet-derived growth factor receptor beta; <i>PIK3C2α</i>: phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 alpha; <i>PIK3R2</i>: phosphoinositide-3-kinase regulatory subunit 2; <i>PRMT1</i>: protein arginine methyltransferase 1; <i>PUMA</i>: p53 upregulated modulator of apoptosis; <i>RHEB</i>: Ras homolog, mTORC1 binding; <i>RICTOR</i>: RPTOR-independent companion of mTOR, complex 2; <i>ROCK2</i>: Rho-associated coiled-coil containing protein kinase 2; <i>SDF1</i>: Stromal cell-derived factor 1; <i>SETDB1</i>: SET domain bifurcated histone lysine methyltransferase 1; <i>SIAT1</i>: Siah E3 ubiquitin protein ligase 1; <i>SIRT1</i>: Sirtuin 1; <i>SIX1</i>: SIX homeobox 1; <i>SMAD1</i>: SMAD family member 1; <i>SMAD2</i>: SMAD family member 2; <i>SMAD3</i>: SMAD family member 3; <i>SOX2</i>: sex-determining region Y-box 2; <i>SPI1</i>: Transcription factor Sp1 (specificity protein 1); <i>SREBP-1c</i>: Sterol regulatory element binding protein-1c; <i>STAT3</i>: signal transducer and activator of transcription 3; <i>STMN1</i>: Stathmin 1; <i>TAB3</i>: TGF beta-activated kinase binding protein 3; <i>TAK1</i>: Transforming growth factor beta-activated kinase 1; <i>TGFβ1</i>: Transforming growth factor beta 1; <i>TGFβRI</i>: Transforming growth factor beta receptor 1; <i>TNFRF6B</i>: Tumor necrosis factor receptor super family 6B; <i>TNIP2</i>: TNFAIP3 interacting protein 2; <i>VEGFR</i>: vascular endothelial growth factor receptor; <i>ZEB2</i>: Zinc finger E-box binding homeobox 2; <i>ZHX1</i>: Zinc fingers and homeobox 1.</p>				

(lncRNAs). lncRNAs are a bit longer than miRNAs with a transcript length of more than 200 nucleotides [133]. lncRNAs have been extensively researched for their role in HCC pathogenesis and their therapeutic potential. As will be expounded shortly, a number of lncRNAs function by what is known as miRNA sponges, which basically involves buffering the action of miRNAs on their target mRNAs.

Given the comprehensive nature of this review, only some of the most recent reports involving lncRNA in HCC are discussed below. However, detailed information about earlier reports can be found in the following reviews: [134–136]. Additionally, the following bibliographic data [134–214] afford an extensive exposition of the most recent HCC lncRNA-oriented work. Beside the compendious run-through below, Table 5 affords an encyclopedic overview of the lncRNAs studied in these resources which were not discussed in the text for practical reasons.

6.8. GAS8-AS1. It was recently reported that both the *GAS8* gene and its resident lncRNA, *GAS8-AS1*, act as tumor suppressors and manifest a significantly low expression in HCC tissues, which correlated with poor prognosis [157]. *GAS8-AS1* was curiously found to mediate the transcription of *GAS8*. It was essential in maintaining chromatin in an uncondensed state by recruiting the H3K4 methyltransferase *MLL1* and its accessory protein *WD-40 repeat protein 5* (*WDR5*). This leads to the potentiation of RNA polymerase II and enhanced transcription of *GAS8*. The above molecular events suppressed oncogenesis and impeded HCC development.

6.9. FENDRR. *FOXF1 adjacent noncoding developmental regulatory RNA* (*FENDRR*), another lncRNA that was found to be downregulated in HCC, was recently advocated as a potential therapeutic approach to arrest HCC progression and discourage metastasis. Ectopic expression of *FENDRR* was reported to check malignant growths *in vitro* and *in vivo*, as well as repressing HCC migration and invasion. This was purported to occur via epigenetic regulation of *glypican-3* (*GPC3*). Through interacting with the *GPC3* promoter and subsequently leading to its methylation, *FENDRR* functions to silence *GPC3*, counteracting the latter's oncogenic effects [168].

6.10. CASC2c. *Cancer susceptibility candidate 2c* (*CASC2c*) is one of three lncRNA transcripts produced by the alternative splicing of *cancer susceptibility 2* (*CASC2*). Inherently silenced in HCC, the overexpression of *CASC2c* resulted in the suppression of proliferation of HCC cells, while inducing apoptosis. These effects coincided with lowered phosphorylated *extracellular signal-regulated kinase 1/2* (*p-ERK1/2*) and β -catenin levels [201].

6.11. miR503HG. *miR503HG*, the host gene of *miR-503* (see above), has been found to be significantly downregulated in HCC [141]. This silencing was closely related to survival rates and duration until tumor recurrence and is thus conjectured to be a prognostic biomarker. The gain of function abrogated the invasion and metastasis of HCC cells. *miR503HG* was also found to promote the degradation of the *heterogeneous*

nuclear ribonucleoprotein A2/B1 (*HNRNPA2B1*) by ubiquitination and subsequent proteasomal degradation, which consequently led to the destabilization of *p52* and *p65* transcripts and ultimately suppressed *NF- κ B* signaling in HCC. Given their innate interplay and their common effect on HCC cells, *miR503HG* and its resident microRNA (*miR-503*) could cooperatively function to stymie migration of HCC cells.

6.12. LINC00467. *LINC00467*, another lncRNA that was found to be downregulated in HCC, has been studied as a potential therapeutic target thanks to its role as an antagomir for *miR-9-5a*, which targets *peroxisome proliferator-activated receptor alpha* (*PPARA*) for silencing [140]. *LINC00467* ectopically expressed in HCC cells conducted to antiproliferative effects and, like *miR503HG*, checked migration and invasion. The authors propose a pivotal implication of the *LINC00467/miR-9-5p/PPARA* loop in the initiation and progression of HCC.

6.13. Linc-GALH and UC001kfo. Contrary to the above-mentioned lncRNAs, which are downregulated in HCC and which are considered tumor suppressors, other lncRNAs are oncogenic, with anomalously high expression in HCC. *Linc-GALH* and *UC001kfo* were recently reported to be upregulated in HCC. *Linc-GALH* was surmised to regulate methylation of *Gankyrin* and hence its expression [190]. Mechanistically, this was proposed to occur via deubiquitinating DNMT1. This promoted migration and invasion in HCC cells and was rescinded in silencing experiments. Increased expression of *UC001kfo* correlated with tumoral macrovascular invasion (MVI) and TNM staging of HCC, with higher levels predisposing to poorer prognoses [179]. *UC001kfo* boosted tumor proliferation and EMT, presumably through targeting *alpha-smooth muscle actin* (α -SMA). The authors indicate the potential of *UC001kfo* to serve as a prognostic marker as well as a target for therapy.

6.14. LINC00346. *LINC00346* was shown to be aberrantly upregulated in HCC [139]. *LINC00346* enhanced the expression of *WD Repeat Domain 18* (*WDR18*) by virtue of competitively binding to *miR-542-3p*, a downregulated tumor suppressor in HCC cells. This sponging effect leads to the activation of the *Wnt/ β -catenin* pathway. As such, *LINC00346* could be a viable target in HCC therapy, where its inhibition is presumed to unmask the anticancer effects of *miR-542-p*.

6.15. LINC00978. Both tumor tissues and serum samples from HCC patients manifested an exaggerated expression of *LINC00978* [69]. Serum levels of this lncRNA could even distinguish between HCC patients and patients with hepatitis or cirrhosis. *LINC00978* was reported to promote cellular proliferation, migration, and invasion, wherein its knock-down arrested the cell cycle and encouraged apoptosis. The authors unveiled the mechanistic basis of such effects to involve binding of *LINC00978* to *EZH2*, leading to its buildup at the promoter regions of *E-cadherin* and *p21* genes, which leads to these genes becoming silenced subsequent of *EZH2*-mediated H27K3 trimethylation. The validity of this regulatory circuit was confirmed by the abrogation of

TABLE 5: Dysregulated long noncoding RNAs (lncRNAs) in HCC. Long noncoding RNAs are shown with the trend of dysregulation associated with HCC. As is evident, the majority of dysregulated lncRNAs follow an upward tendency. Also evident is the involvement of lncRNA-mediated miRNA sponging in producing the oncogenic molecular phenotypes.

lncRNA	Expression in HCC	Effect of dysregulation	Ref.
<i>91H</i>	Upregulated	Promoting tumor growth and metastasis; upregulation of <i>IGF2</i> , H3K4me3, and H3K27me3 at the P3 and P4 promoters	[208]
<i>AC006262.5</i>	Upregulated	Inhibition of <i>miR-7855-5p</i> and upregulation of <i>BPY2C</i>	[200]
<i>AC092171.4</i>	Upregulated	Inhibition of <i>miR-1271</i> and upregulation of <i>GRB2</i>	[182]
<i>ANCR</i>	Upregulated	Enhanced proliferation and EMT; upregulation of <i>HNRNPA1</i> through <i>miR-140-3p</i> sponging	[151]
<i>ANRIL</i>	Upregulated	Inhibition of <i>miR-384</i> and upregulation of <i>STAT3</i>	[214]
<i>ASMTL-AS1</i>	Upregulated	Upregulation of <i>NLK</i> and activation of YAP signaling via <i>miR-342-3p</i> sponging	[293]
<i>CASC2c</i>	Downregulated	Activation of <i>ERK1/2</i> and <i>Wnt/β-catenin</i> signaling	[201]
<i>CASC15</i>	Upregulated	Activation of <i>Wnt/β-catenin</i> signaling via upregulation of <i>SOX4</i>	[196]
<i>CRNDE</i>	Upregulated	Inhibition of the <i>Hippo</i> pathway	[210]
<i>CTBP1-AS2</i>	Upregulated	Sponging of <i>miR-195-5p</i> and enhancing <i>CEP55</i> expression	[198]
<i>DANCR</i>	Upregulated	Enhanced cell proliferation, colony formation, and autophagy; upregulation of <i>ATG7</i> and suppression of <i>miR-222-3p</i>	[188]
<i>DDX11-AS1</i>	Upregulated	Inhibition of <i>LATS2</i> expression via <i>EZH2</i> and <i>DNMT1</i>	[203, 204, 207]
<i>DUXAP8</i>	Upregulated	Enhanced cell proliferation and EMT; <i>miR-422a</i> sponging and upregulation of <i>PKD2</i>	[147]
<i>FENDRR</i>	Downregulated	Downregulation of <i>GPC3</i>	[168]
<i>FOXD2-AS1</i>	Upregulated	<i>miR-206</i> sponging and enhanced <i>MAP3K1</i> signaling	[174]
<i>FOXD3-AS1</i>	Upregulated	<i>miR-335</i> sponging and upregulation of <i>RICTOR</i>	[159]
<i>GAS8-AS1</i>	Downregulated	Attenuated <i>GAS8</i> transcription RNA polymerase II activity	[157]
<i>H19</i>	Upregulated	Amelioration of resistance to sorafenib and upregulation of <i>miR-675</i>	[177]
<i>HAND2-AS1</i>	Downregulated	Enhanced proliferation; upregulation of <i>miR-300</i> and inhibition of <i>SOC5</i>	[155]
<i>HBVPTPAP</i>	Upregulated	Activation of <i>JAK/STAT</i> signaling	[186]
<i>HCG18</i>	Upregulated	Upregulation of <i>CENPM</i> via sponging of <i>miR-214-3p</i>	[180]
<i>HEIH</i>	Downregulated	Suppression of cell proliferation and metastasis; upregulation of <i>miR-199a-3p</i>	[169]
<i>HLNC1</i>	Upregulated	Destabilization of <i>USP49</i>	[183]
<i>HOTAIR</i>	Upregulated	Downregulation of <i>c-Met</i> and <i>miR-34a</i>	[178, 184]
<i>HOXA11-AS</i>	Upregulated	Downregulation of <i>miR-506-3p</i> and <i>Slug</i>	[191]
<i>KCNQ1OT1</i>	Upregulated	Upregulation of <i>ACER3</i> via sponging of <i>miR-146a-5p</i> ; enhanced sorafenib resistance and <i>PD-L1</i> -mediated immune escape via <i>miR-506</i> sponging	[197, 205]
<i>LALR1</i>	Upregulated	Anaplasia and distant metastases; upregulation of <i>SNORD72</i>	[154]
<i>LEF1-AS1</i>	Upregulated	Enhancement of tumor growth and chemoresistance; inhibition of <i>miR-10a-5p</i> and upregulation of <i>MSI</i> , <i>CDCA7</i> , and <i>EZH2</i>	[162, 194]
<i>LINC00160</i>	Upregulated	Inhibition of <i>miR-132</i> and elevated levels of <i>PIK3R3</i>	[144]
<i>LINC00174</i>	Upregulated	Enhanced proliferation and metastasis and decreased apoptosis; sponging of <i>miR-320</i> and upregulation of <i>S100A10</i>	[152]
<i>LINC00467</i>	Downregulated	Sponging of <i>miR-9-5a</i> and consequent upregulation of <i>PPARA</i>	[140]
<i>LINC00662</i>	Upregulated	Posttranscriptional inhibition of <i>NR4A3</i>	[153]
			[294]

TABLE 5: Continued.

IncRNA	Expression in HCC	Effect of dysregulation	Ref.
		Genome-wide hypomethylation; modulation of <i>MAT1A/SAM</i> and <i>AHCY/SAH</i> interactions, leading to reduced <i>SAM</i> and increased <i>SAH</i>	
<i>LINC00668</i>	Upregulated	Promoting cell proliferation and EMT; sponging of <i>miR-532-5p</i> and consequent upregulation of <i>YY1</i>	[161]
<i>LINC00978</i>	Upregulated	Inhibition of <i>p21</i> and <i>E-cadherin</i> via <i>EZH2</i> -mediated silencing	[211]
<i>LINC01224</i>	Upregulated	Inhibition of <i>miR-330-5p</i> and consequent upregulation of <i>CHEK1</i>	[212]
<i>LINC01278</i>	Upregulated	Promoting metastasis; inhibition of <i>miR-1258</i>	[164]
<i>LINC01296</i>	Upregulated	Positive regulation of the <i>miR-26a/PTEN</i> axis	[137]
<i>LINC01419</i>	Upregulated	Histone methylation of the <i>RECK</i> promoter via <i>EZH2</i>	[173]
<i>Linc-GALH</i>	Downregulated	Upregulation of <i>Gankyrin</i>	[190]
<i>IncARSR</i>	Upregulated	Reduction of <i>YAP1</i> phosphorylation and activation of <i>IRS2/AKT</i> signaling	[156]
<i>IncRNA-POIR</i>	Upregulated	Enhanced EMT and sorafenib resistance; sponging of <i>miR-182-5p</i>	[202]
<i>MALAT1</i>	Upregulated	Tumor progression and doxorubicin resistance; <i>miR-3129-5p</i> sponging, upregulation of β -catenin	[199, 209]
<i>MF12-AS1</i>	Upregulated	Improved proliferation and metastasis; sponging of <i>miR-134</i> and upregulation of <i>FOXM1</i>	[142]
<i>MINCR</i>	Upregulated	Enhanced proliferation and inhibition of apoptosis; downregulation of <i>miRNA-107</i>	[150]
<i>miR503HG</i>	Downregulated	Enhanced invasion and metastasis; activation of <i>NF-κB</i> signaling	[141]
<i>MSC-AS1</i>	Upregulated	Promoting cell proliferation and colony formation; suppression of <i>PGK1</i>	[172]
<i>MT1JP</i>	Downregulated	Repression of tumor growth; decreased <i>AKT</i> expression	[170]
<i>NEAT1</i>	Upregulated	Upregulation of <i>WEE1</i> through <i>miR-101-3p</i> sponging; inhibition of <i>miR-129-5p</i>	[129, 138]
<i>OIP5-AS1</i>	Upregulated	Promoting cell proliferation, migration and angiogenesis. Inhibition of apoptosis; inhibition of the <i>miR-26a-3p</i> and <i>miR-3163</i>	[163, 171]
<i>OTUD6B-AS1</i>	Upregulated	Enhanced proliferation and colony formation; sponging of <i>miR-664b-3p</i>	[181]
<i>PICSA</i>	Upregulated	Enhanced proliferation and colony formation; sponging of <i>miR-588</i>	[189]
<i>RHPN1-AS1</i>	Upregulated	Promoting proliferation, migration and invasion; suppression of <i>miR-485-5p</i>	[165]
<i>RUNX1-IT1</i>	Downregulated	Desponging of <i>miR-632</i> and activation of <i>WNT/β-catenin</i> pathway	[148]
<i>RUSC1-AS1</i>	Upregulated	Enhanced proliferation and reduced apoptosis; <i>miR-7-5p</i> sponging and upregulation of <i>NOTCH3</i>	[185]
<i>SLC2A1-AS1</i>	Downregulated	Suppression of glycolysis in HCC cells; downregulation of <i>GLUT1</i>	[158]
<i>SNAT3-AS1</i>	Upregulated	Promoting proliferation and metastasis; activation of <i>PEG10</i> sponging <i>miR-27-3p</i> and <i>miR-34a-5p</i>	[195]
<i>SNHG1</i>	Upregulated	Enhanced tumor progression and metastasis; sponging of <i>miR-377-3p</i>	[149]
<i>SNHG5</i>	Upregulated	Sponging of <i>miR-26a-5p</i> and upregulation of the downstream target, <i>RNF38</i>	[160]
<i>SNHG14</i>	Upregulated	Inhibition of <i>miR-656-3p</i> , promotion of migration and invasion	[176, 187]
<i>SOX2OT</i>	Upregulated	Promoting the Warburg effect and metastasis; upregulation of <i>PKM2</i> via <i>miR-122-5p</i> inhibition	[167]
<i>SUMOIP3</i>	Upregulated	Enhanced cell proliferation and lymph node metastasis; <i>miR-320a</i> sponging and activation of <i>Wnt/β-catenin</i> signaling	[146]
<i>TCL6</i>	Downregulated	Activation of <i>PI3K/AKT</i> signaling via upregulation of <i>miR-106a-5p</i>	[145]
<i>TMPO-AS1</i>	Upregulated	Promoting proliferation, migration, and invasion; <i>miR-329-3p</i> sponging	[166]
<i>TUG1</i>	Upregulated	Negative regulation of <i>miR-137</i> and <i>AKT2</i> and promoting EMT	[175]
<i>UBE2R2-AS1</i>	Upregulated	<i>miR-302b</i> sponging and upregulation of <i>EGFR</i>	[192]
<i>UC001kfo</i>	Upregulated	Enhanced proliferation, macrovascular invasion, and EMT; upregulation of α -SMA	[179]

TABLE 5: Continued.

lncRNA	Expression in HCC	Effect of dysregulation	Ref.
<i>ZFAS1</i>	Upregulated	Enhanced proliferation; <i>miR-193a-3p</i> suppression	[213]
<i>ZFPM2-AS1</i>	Upregulated	Enhanced proliferation, migration, and invasion; inhibition of <i>miR-139</i>	[193]
<i>ZNF281</i>	Upregulated	Promoting migration and invasion; downregulation of <i>miR-539</i>	[143]

ACER3: Alkaline Ceramidase 3; *AHCY*: Adenosylhomocysteinase; *AKT*: Protein kinase B; *ATG7*: Autophagy-related 7; *BPY2C*: Basic Charge Y-Linked 2C; *CDC47*: Cell Division Cycle-Associated 7; *CENPM*: Centromere Protein M; *CEP55*: Centrosomal Protein 55; *CHEK1*: checkpoint kinase 1; *c-Met*: Tyrosine-protein kinase *Met*; *DNM1T1*: DNA methyltransferase 1; *EGFR*: epidermal growth factor receptor; *ERK*: extracellular signal-regulated kinase; *EZH2*: enhancer of zeste homolog 2; *FOXMI*: Forkhead box protein M1; *GAS8*: growth arrest-specific 8; *GLUT1*: Glucose transporter 1; *GPC3*: Glypican 3; *GRB2*: growth factor receptor-bound protein 2; *HNRNP1A1*: heterogeneous nuclear ribonucleoprotein A1; *IGF2*: insulin-like growth factor 2; *IRS2*: *insulin receptor substrate* 2; *JAK*: Janus kinase; *LATS2*: large tumor suppressor 2; *MAP3K1*: mitogen-activated protein kinase 1; *MAT1A*: Methionine Adenosyltransferase 1A; *MSI*: RNA-binding protein Musashi; *NF-κB*: nuclear factor kappa-light-chain-enhancer of activated B cells; *NLK*: Nemo-Like Kinase; *NOTCH3*: Notch Receptor 3; *NR4A3*: Nuclear Receptor Subfamily 4 Group A Member 3; *p21*: cyclin-dependent kinase inhibitor 1; *PDK2*: Pyruvate dehydrogenase kinase isoform 2; *PD-L1*: Programmed death-ligand 1; *PEG10*: Paternally Expressed 10; *PGK1*: Phosphoglycerate Kinase 1; *PI3K*: Phosphoinositide 3-kinase; *PIK3R3*: Phosphoinositide-3-Kinase Regulatory Subunit 3; *PKM2*: Pyruvate kinase muscle isozyme; *PPARA*: peroxisome proliferator-activated receptor alpha; *P7EN*: Phosphatase and tensin homolog; *RECK*: Reversion-inducing-cysteine-rich protein with kazal motifs; *RICTOR*: Rapamycin-insensitive companion of mammalian target of rapamycin; *RNF38*: Ring Finger Protein 38; *S100A10*: S100 Calcium Binding Protein A10; *SAH*: S-adenosyl homocysteine; *SAM*: S-adenosyl-L-methionine; *SNORD72*: Small Nucleolar RNA, C/D Box 72; *SOC5*: Suppressor of cytokine signaling 5; *SOX4*: SRY-Box Transcription Factor 4; *STAT3*: signal transducer and activator of transcription 3; *USP49*: Ubiquitin-Specific Peptidase 49; *WEE1*: WEE1 G2 Checkpoint Kinase; *YAP/YAPI*: Yes-associated protein 1; *YY1*: Yin Yang 1; *α-SMA*: *alpha*-smooth muscle actin.

LINC00978 knockdown's inhibitory effects in *E-cadherin* and *p21* knockdowns.

6.16. *NEAT1*. Nuclear-enriched abundant transcript 1 (*NEAT1*) is another lncRNA that is upregulated in HCC [138]. Silencing of *NEAT1* compromised cell viability and was shown to be proapoptotic in HepG2 and Huh7 cells. Again, as with other lncRNA/miRNA-negative correlations, *NEAT1* exhibited an opposite trend of expression to *miR-129-5p* in HCC. Ectopic expression of *NEAT1* suppressed *miR-129-5p* via modulating the *valosin-containing protein* (*VCP*)/*I κ B* axis to the overall result of encouraging cellular proliferation.

6.17. *ANRIL*, *LINC01296*, and *LINC01224*. Similarly, antisense noncoding RNA in the *INK4* locus (*ANRIL*), *LINC01296*, and *LINC01224* were all overexpressed in HCC and mediated their oncogenic effects through inhibition of microRNA signaling axes. *ANRIL*'s prooncogenic effects were found to rely on its suppression of *miR-384*, which targets *signal transducer and activator of transcription 3* (*STAT3*) [214]. These correlations were observed both *in vitro* and *in vivo*. *LINC01296* regulated the *miR-26a/PTEN* axis, resulting in tumor progression also *in vitro* and *in vivo* [137]. Similarly, an upswing of *LINC01224* in HCC was correlated with a silenced *miR-330-5p* and a consequent upregulation of its target, *checkpoint kinase 1* (*CHEK1*) [212]. *LINC01224* knockdowns exhibited a concurrent downregulation of *CHEK1*, owing to its binding to and inhibition of *miR-330-5p*, leading to tumor regression.

6.18. *ZFAS1*. HCC tissues exhibited an increased level of *ZFAS1*, compared to neighboring normal tissues [69]. The proliferative capacity of the tumor was substantially compromised subsequent of *ZFAS1* silencing, and its overexpression had a gainful effect on tumor growth. The authors report that the tumor suppressor miRNA, *miR-193a-3p*, was elevated in *ZFAS1* knockdowns which, confirmed by luciferase reporter assay and correlation analysis, suggested that the prooncogenic role of *ZFAS1* relied on the suppression of *miR-193a-3p*.

6.19. *CRNDE*. The colorectal neoplasia differentially expressed (*CRNDE*) lncRNA has recently been proven to be yet another prooncogenic lncRNA in HCC [210]. Its overexpression was associated with an enhanced proliferative and migratory competence of HCC cells, not to mention an ameliorated resistance to chemotherapy. *CRNDE* was determined to inhibit the Hippo pathway and encourage the *EZH2*-, *SUV39H1*-, and *SUZ12*-mediated inhibition of tumor suppressor genes viz. *large tumor suppressor 2* (*LATS2*) and *CUGBP Elav-like family member 2* (*CELF2*).

6.20. *MALAT1*. *MALAT1* is a notoriously tumorigenic lncRNA implicated in many cancers. Recently, Chang et al. [209] proposed exploiting a *MALAT1/Wnt* regulatory loop for therapeutic purposes in HCC. They reported that *MALAT1* knockdowns evidenced a suppression of canonical *Wnt* signaling and impaired tumorsphere formation, which was coincident with a decline in CD90+ and CD133+ cells,

which consolidated the hypothesis that *MALAT1* plays a vital role in promoting stemness in HCC cells.

7. Future Perspective

Despite the thorough study of epigenetic modulators, their extension to the clinical setting stands far from realizable. Further research mindful of the efficacy versus long-term toxicity/of these alternative strategies should be advocated. Studies looking into the pharmacokinetics of these agents as well as others seeking efficient targeted delivery with minimal systemic side effects are warranted. Addressing the adaptability of these modes of treatment to the clinic can bring us a long way, especially with the dosing curtailment of the highly toxic agents afforded by the concomitant use of the suggested alternatives, which, in some instances, may completely replace current debilitating treatments. As was mentioned, various exploratory clinical studies were carried out, but these need to be seen through to subsequent trial phases and on larger populations. Fortunately, the possible risk posed by a preponderance of these modulators is not significant to impede but should embolden such undertakings.

In addition to the clinical application, endeavors oriented to further our understanding of the elaborate epigenome and its regulation remain imperative. New epigenetic mechanisms are still being discovered contemporarily and progress in the field could do with pursuing modulators of these and assessing their benefits over the already defined ones. For example, decreased crotonylation of histone lysines has been recently incriminated in the progression of HCC [215]. This discovery should prompt several spin-offs in which the enhancers of crotonylation are suggested and assessed for therapeutic utility. Several defined modulatory agents such as histone demethylases (specifically Jumonji lysine demethylases) and helicases (*HELLS*) [216] among others also remain underresearched in HCC and should thus constitute a future research direction in HCC therapeutics.

8. Conclusion

The modulation of the altered epigenome in HCC is a promising therapeutic strategy. Verified potency and tenability to formulation demands for maximal systemic effects render many of the hereinabove nominated agents an intriguing recourse that could be subsequently implemented in clinical settings as a standalone curative or a potentiating adjuvant. It would also remain of equal importance to examine if these modulators can act in parallel to attenuate metastasis. More importantly, validating the use of these modulators in the treatment of HCC with different etiologies will aid in paving the road for personalized medicine together with the advancements in the pharmacogenomics/pharmacogenetics field. This holistic approach is forecasted to lower the success barrier, at least in part, in the treatment of HCC.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

- [1] M. Sayiner, P. Golabi, and Z. M. Younossi, "Disease burden of hepatocellular carcinoma: a global perspective," *Digestive Diseases and Sciences*, vol. 64, no. 4, pp. 910–917, 2019.
- [2] A. K. Singh, R. Kumar, and A. K. Pandey, "Hepatocellular carcinoma: causes, mechanism of progression and biomarkers," *Current chemical genomics and translational medicine*, vol. 12, no. 1, pp. 9–26, 2018.
- [3] L. Ma, M.-S. Chua, O. Andrisani, and S. So, "Epigenetics in hepatocellular carcinoma: an update and future therapy perspectives," *World Journal of Gastroenterology*, vol. 20, no. 2, pp. 333–345, 2014.
- [4] J. I. Martin-Subero and M. Esteller, "Epigenetic mechanisms in cancer development," in *The Molecular Basis of Human Cancer*, pp. 263–275, Springer, New York, 2016.
- [5] M. A. Dawson and T. Kouzarides, "Cancer epigenetics: from mechanism to therapy," *Cell*, vol. 150, no. 1, pp. 12–27, 2012.
- [6] Y.-F. Zheng, X. Lu, X.-Y. Zhang, and B.-G. Guan, "The landscape of DNA methylation in hepatocellular carcinoma," *Journal of Cellular Physiology*, vol. 234, no. 3, pp. 2631–2638, 2018.
- [7] T. H. Bestor, "The DNA methyltransferases of mammals," *Human Molecular Genetics*, vol. 9, no. 16, pp. 2395–2402, 2000.
- [8] K. D. Robertson, "DNA methylation and human disease," *Nature Reviews Genetics*, vol. 6, no. 8, pp. 597–610, 2005.
- [9] T. S. Han, H. S. Ban, K. Hur, and H. S. Cho, "The epigenetic regulation of HCC metastasis," *International Journal of Molecular Sciences*, vol. 19, no. 12, p. 3978, 2018.
- [10] G. Egger, S. Jeong, S. G. Escobar et al., "Identification of DNMT1 (DNA methyltransferase 1) hypomorphs in somatic knockouts suggests an essential role for DNMT1 in cell survival," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 38, pp. 14080–14085, 2006.
- [11] D. Subramaniam, R. Thombre, A. Dhar, and S. Anant, "DNA methyltransferases: a novel target for prevention and therapy," *Frontiers in Oncology*, vol. 4, 2014.
- [12] K. D. Robertson, E. Uzvolgyi, G. Liang et al., "The human DNA methyltransferases (DNMTs) 1, 3a and 3b: coordinate mRNA expression in normal tissues and overexpression in tumors," *Nucleic Acids Research*, vol. 27, no. 11, pp. 2291–2298, 1999.
- [13] K. Revill, T. Wang, A. Lachenmayer et al., "Genome-wide methylation analysis and epigenetic unmasking identify tumor suppressor genes in hepatocellular carcinoma," *Gastroenterology*, vol. 145, no. 6, pp. 1424–1435.e25, 2013.
- [14] I. Martinez-Quetglas, R. Pinyol, D. Dauch et al., "IGF2 is up-regulated by epigenetic mechanisms in hepatocellular carcinomas and is an actionable oncogene product in experimental models," *Gastroenterology*, vol. 151, no. 6, pp. 1192–1205, 2016.
- [15] F. Xu, C. H. Li, C. H. Wong et al., "Genome-wide screening and functional analysis identifies tumor suppressor long non-coding RNAs epigenetically silenced in hepatocellular carcinoma," *Cancer Research*, vol. 79, no. 7, pp. 1305–1317, 2019.
- [16] D. P. F. Tsang, W. K. K. Wu, W. Kang et al., "Yin Yang 1-mediated epigenetic silencing of tumour-suppressive micro-RNAs activates nuclear factor- κ B in hepatocellular carcinoma," *The Journal of Pathology*, vol. 238, no. 5, pp. 651–664, 2016.
- [17] C.-M. Wong, L. Wei, C.-T. Law et al., "Up-regulation of histone methyltransferase SETDB1 by multiple mechanisms in hepatocellular carcinoma promotes cancer metastasis," *Hepatology*, vol. 63, no. 2, pp. 474–487, 2016.
- [18] M. Okano, S. Takebayashi, K. Okumura, and E. Li, "Assignment of cytosine-5 DNA methyltransferases *Dnmt3a* and *Dnmt3b* to mouse chromosome bands 12A2–A3 and 2H1 by in situ hybridization," *Cytogenetic and Genome Research*, vol. 86, no. 3–4, pp. 333–334, 1999.
- [19] G. L. Xu, T. H. Bestor, D. Bourc'his et al., "Chromosome instability and immunodeficiency syndrome caused by mutations in a DNA methyltransferase gene," *Nature*, vol. 402, no. 6758, pp. 187–191, 1999.
- [20] L. Di Croce, V. A. Raker, M. Corsaro et al., "Methyltransferase recruitment and DNA hypermethylation of target promoters by an oncogenic transcription factor," *Science*, vol. 295, no. 5557, pp. 1079–1082, 2002.
- [21] B.-K. Oh, H. Kim, H.-J. Park et al., "DNA methyltransferase expression and DNA methylation in human hepatocellular carcinoma and their clinicopathological correlation," *International Journal of Molecular Medicine*, vol. 20, no. 1, pp. 65–73, 2007.
- [22] H. Li, T. Rauch, Z. X. Chen, P. E. Szabó, A. D. Riggs, and G. P. Pfeifer, "The histone methyltransferase SETDB1 and the DNA methyltransferase DNMT3A interact directly and localize to promoters silenced in cancer cells," *The Journal of Biological Chemistry*, vol. 281, no. 28, pp. 19489–19500, 2006.
- [23] M. H. Lee, H. Na, T. Y. Na, Y. K. Shin, J. K. Seong, and M. O. Lee, "Epigenetic control of metastasis-associated protein 1 gene expression by hepatitis B virus X protein during hepatocarcinogenesis," *Oncogene*, vol. 1, no. 9, 2012.
- [24] J. Yu, X. Yuan, L. Sjöholm et al., "Telomerase reverse transcriptase regulates DNMT3B expression/aberrant DNA methylation phenotype and AKT activation in hepatocellular carcinoma," *Cancer Letters*, vol. 434, pp. 33–41, 2018.
- [25] H. Fan, L. Chen, F. Zhang et al., "MTSS1, a novel target of DNA methyltransferase 3B, functions as a tumor suppressor in hepatocellular carcinoma," *Oncogene*, vol. 31, no. 18, pp. 2298–2308, 2012.
- [26] Z. Zhao, Q. Wu, J. Cheng, X. Qiu, J. Zhang, and H. Fan, "Depletion of DNMT3A suppressed cell proliferation and restored PTEN in hepatocellular carcinoma cell," *Journal of Biomedicine & Biotechnology*, vol. 2010, 10 pages, 2010.
- [27] G. Szpatecki, T. Ilczuk, D. Wolosz, W. Otto, and B. Gornicka, "The expression of DNA methyltransferase DNMT3a in classical and fibrolamellar hepatocellular carcinoma," *Journal of Clinical and Experimental Pathology*, vol. 6, no. 3, 2016.
- [28] M. S. Kareta, Z. M. Botello, J. J. Ennis, C. Chou, and F. Chédin, "Reconstitution and mechanism of the stimulation of de novo methylation by human DNMT3L," *The Journal of Biological Chemistry*, vol. 281, no. 36, pp. 25893–25902, 2006.
- [29] L. Gailhouse, L. C. Liew, K. Yasukawa et al., "Differentiation therapy by epigenetic reconditioning exerts antitumor effects on liver cancer cells," *Molecular Therapy*, vol. 26, no. 7, pp. 1840–1854, 2018.
- [30] S. O. Sajadian, S. Ehnert, H. Vakilian et al., "Induction of active demethylation and 5hmC formation by 5-azacytidine is TET2 dependent and suggests new treatment strategies

- against hepatocellular carcinoma,” *Clinical Epigenetics*, vol. 7, no. 1, p. 98, 2015.
- [31] Y. K. Hong, Y. Li, H. Pandit et al., “Epigenetic modulation enhances immunotherapy for hepatocellular carcinoma,” *Cellular Immunology*, vol. 336, pp. 66–74, 2019.
- [32] S. O. Sajadian, C. Tripura, F. S. Samani et al., “Vitamin C enhances epigenetic modifications induced by 5-azacytidine and cell cycle arrest in the hepatocellular carcinoma cell lines HLE and Huh7,” *Clinical Epigenetics*, vol. 8, no. 1, p. 46, 2016.
- [33] A. Ilyas, Z. Hashim, and S. Zarina, “Effects of 5'-azacytidine and alendronate on a hepatocellular carcinoma cell line: a proteomics perspective,” *Molecular and Cellular Biochemistry*, vol. 405, no. 1–2, pp. 53–61, 2015.
- [34] M. Sanaei, F. Kavooosi, and Z. Esmi, “The effect of 5-aza-2'-deoxycytidine in combination to and in comparison with vorinostat on DNA methyltransferases, histone deacetylase 1, glutathione S-transferase 1 and suppressor of cytokine signaling 1 genes expression, cell growth inhibition and apoptotic induction in hepatocellular LCL-PI 11 cell line,” *International Journal of Hematology-Oncology and Stem Cell Research*, vol. 14, no. 1, pp. 45–55, 2020.
- [35] S.-I. Suh, H.-Y. Pyun, J.-W. Cho et al., “5-Aza-2'-deoxycytidine leads to down-regulation of aberrant p16INK4A RNA transcripts and restores the functional retinoblastoma protein pathway in hepatocellular carcinoma cell lines,” *Cancer Letters*, vol. 160, no. 1, pp. 81–88, 2000.
- [36] B. Lin, X. Zhou, S. Lin et al., “Epigenetic silencing of PRSS3 provides growth and metastasis advantage for human hepatocellular carcinoma,” *Journal of Molecular Medicine*, vol. 95, no. 11, pp. 1237–1249, 2017.
- [37] Q. Mei, M. Chen, X. Lu et al., “An open-label, single-arm, phase I/II study of lower-dose decitabine based therapy in patients with advanced hepatocellular carcinoma,” *Oncotarget*, vol. 6, no. 18, pp. 16698–16711, 2015.
- [38] S. Jueliger, J. Lyons, S. Cannito et al., “Efficacy and epigenetic interactions of novel DNA hypomethylating agent guadecitabine (SGI-110) in preclinical models of hepatocellular carcinoma,” *Epigenetics*, vol. 11, no. 10, pp. 709–720, 2016.
- [39] Y. Kuang, A. El-Khoueiry, P. Taverna, M. Ljungman, and N. Neamati, “Guadecitabine (SGI-110) priming sensitizes hepatocellular carcinoma cells to oxaliplatin,” *Molecular Oncology*, vol. 9, no. 9, pp. 1799–1814, 2015.
- [40] A. Gnyszk, Z. Jastrzebski, and S. Flis, “DNA methyltransferase inhibitors and their emerging role in epigenetic therapy of cancer,” *Anticancer Research*, vol. 33, no. 8, pp. 2989–2996, 2013.
- [41] C. Raggi, V. M. Factor, D. Seo et al., “Epigenetic reprogramming modulates malignant properties of human liver cancer,” *Hepatology*, vol. 59, no. 6, pp. 2251–2262, 2014.
- [42] K. Nakamura, K. Aizawa, K. Nakabayashi et al., “DNA methyltransferase inhibitor zebularine inhibits human hepatic carcinoma cells proliferation and induces apoptosis,” *PLoS One*, vol. 8, no. 1, article e54036, 2013.
- [43] M. Sanaei and F. Kavooosi, “Effect of zebularine in comparison to and in combination with trichostatin a on CIP/KIP family (p21Cip1/Waf1/Sdi1, p27Kip1, and p57Kip2), DNMTs (DNMT1, DNMT3a, and DNMT3b), class I HDACs (HDACs 1, 2, 3) and class II HDACs (HDACs 4, 5, 6) gene expression, cell growth inhibition and apoptosis induction in colon cancer LS 174T cell line,” *Asian Pacific Journal of Cancer Prevention*, vol. 21, no. 7, pp. 2131–2139, 2020.
- [44] S. R. Lepri, D. Sartori, S. C. Semperebon, A. Baranoski, G. C. Coatti, and M. S. Mantovani, “Genistein affects expression of cytochrome P450 (CYP450) genes in hepatocellular carcinoma (HEPG2/C3A) cell line,” *Drug Metabolism Letters*, vol. 12, no. 2, pp. 138–144, 2018.
- [45] S. R. Lee, S. W. Kwon, Y. H. Lee et al., “Dietary intake of genistein suppresses hepatocellular carcinoma through AMPK-mediated apoptosis and anti-inflammation,” *BMC Cancer*, vol. 19, no. 1, p. 6, 2019.
- [46] M. Sanaei, F. Kavooosi, A. Roustazadeh, and F. Golestan, “Effect of genistein in comparison with trichostatin A on reactivation of DNMTs genes in hepatocellular carcinoma,” *Journal of Clinical and Translational Hepatology*, vol. 6, no. 2, pp. 141–146, 2018.
- [47] M. Sanaei, F. Kavooosi, and H. Salehi, “Genistein and trichostatin A induction of estrogen receptor alpha gene expression, apoptosis and cell growth inhibition in hepatocellular carcinoma HepG 2 cells,” *Asian Pacific Journal of Cancer Prevention*, vol. 18, no. 12, pp. 3445–3450, 2017.
- [48] S. Bimonte, V. Albino, M. Piccirillo et al., “Epigallocatechin-3-gallate in the prevention and treatment of hepatocellular carcinoma: experimental findings and translational perspectives,” *Drug Design, Development and Therapy*, vol. Volume 13, pp. 611–621, 2019.
- [49] J. L. Won, J. Y. Shim, and B. T. Zhu, “Mechanisms for the inhibition of DNA methyltransferases by tea catechins and bioflavonoids,” *Molecular Pharmacology*, vol. 68, no. 4, pp. 1018–1030, 2005.
- [50] V. S. Thakur, G. Deb, M. A. Babcook, and S. Gupta, “Plant phytochemicals as epigenetic modulators: role in cancer chemoprevention,” *The AAPS Journal*, vol. 16, no. 1, pp. 151–163, 2014.
- [51] S. Li, L. Wu, J. Feng et al., “In vitro and in vivo study of epigallocatechin-3-gallate-induced apoptosis in aerobic glycolytic hepatocellular carcinoma cells involving inhibition of phosphofructokinase activity,” *Scientific Reports*, vol. 6, 2016.
- [52] D. Sabry, O. O. Abdelaleem, A. M. el Amin Ali et al., “Anti-proliferative and anti-apoptotic potential effects of epigallocatechin-3-gallate and/or metformin on hepatocellular carcinoma cells: in vitro study,” *Molecular Biology Reports*, vol. 46, no. 2, pp. 2039–2047, 2019.
- [53] Y. Wen, R.-Q. Zhao, Y.-K. Zhang et al., “Effect of Y6, an epigallocatechin gallate derivative, on reversing doxorubicin drug resistance in human hepatocellular carcinoma cells,” *Oncotarget*, vol. 8, no. 18, pp. 29760–29770, 2017.
- [54] C. L. Peterson and M. A. Laniel, “Histones and histone modifications,” *Current Biology*, vol. 14, no. 14, pp. R546–R551, 2004.
- [55] T. B. Toh, J. J. Lim, and E. K.-H. Chow, “Epigenetics of hepatocellular carcinoma,” *Clinical and Translational Medicine*, vol. 8, no. 1, p. 13, 2019.
- [56] B. Wahid, A. Ali, S. Rafique, and M. Idrees, “New insights into the epigenetics of hepatocellular carcinoma,” *BioMed Research International*, vol. 2017, 16 pages, 2017.
- [57] C. Sawan and Z. Herceg, “Histone modifications and cancer,” *Advances in Genetics*, vol. 70, pp. 57–85, 2010.
- [58] Y. Chervona and M. Costa, “Histone modifications and cancer: biomarkers of prognosis?,” *American Journal of Cancer Research*, vol. 2, no. 5, pp. 589–597, 2012.
- [59] W. Fu, L. Gao, C. Huang et al., “Mechanisms and importance of histone modification enzymes in targeted therapy for

- hepatobiliary cancers," *Discovery medicine*, vol. 28, no. 151, pp. 17–28, 2019.
- [60] S. Y. Roth, J. M. Denu, and C. D. Allis, "Histone acetyltransferases," *Annual Review of Biochemistry*, vol. 70, no. 1, pp. 81–120, 2001.
 - [61] S. Ropero and M. Esteller, "The role of histone deacetylases (HDACs) in human cancer," *Molecular Oncology*, vol. 1, no. 1, pp. 19–25, 2007.
 - [62] M. Haberland, R. L. Montgomery, and E. N. Olson, "The many roles of histone deacetylases in development and physiology: implications for disease and therapy," *Nature Reviews Genetics*, vol. 10, no. 1, pp. 32–42, 2009.
 - [63] K. J. Falkenberg and R. W. Johnstone, "Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders," *Nature Reviews Drug Discovery*, vol. 13, no. 9, pp. 673–691, 2014.
 - [64] E. Ceccacci and S. Minucci, "Inhibition of histone deacetylases in cancer therapy: lessons from leukaemia," *British Journal of Cancer*, vol. 114, no. 6, pp. 605–611, 2016.
 - [65] S. Y. Ler, L. E. N. G. CH, L. W. Khin et al., "HDAC1 and HDAC2 independently predict mortality in hepatocellular carcinoma by a competing risk regression model in a Southeast Asian population," *Oncology Reports*, vol. 34, no. 5, pp. 2238–2250, 2015.
 - [66] J. Yang, X. Jin, Y. Yan et al., "Inhibiting histone deacetylases suppresses glucose metabolism and hepatocellular carcinoma growth by restoring FBP1 expression," *Scientific Reports*, vol. 7, 2017.
 - [67] Y. H. Lee, D. Seo, K. J. Choi et al., "Antitumor effects in hepatocarcinoma of isoform-selective inhibition of HDAC2," *Cancer Research*, vol. 74, no. 17, pp. 4752–4761, 2014.
 - [68] H. Wu, T. Y. Yang, Y. Li et al., "Tumor necrosis factor receptor-associated factor 6 promotes hepatocarcinogenesis by interacting with histone deacetylase 3 to enhance c-Myc gene expression and protein stability," *Hepatology*, vol. 71, no. 1, pp. 148–163, 2020.
 - [69] H. Ji, Y. Zhou, X. Zhuang et al., "HDAC3 deficiency promotes liver cancer through a defect in H3K9ac/H3K9me3 transition," *Cancer Research*, vol. 79, no. 14, pp. 3676–3688, 2019.
 - [70] Y. Hu, Q. Nie, M. Dai, F. Chen, and H. Wu, "Histone deacetylases inhibit the Snail2-mediated EMT during metastasis of hepatocellular carcinoma cells," *Frontiers in Cell and Development Biology*, vol. 8, 2020.
 - [71] Y. Hu, Y. Zheng, M. Dai et al., "G9a and histone deacetylases are crucial for Snail2-mediated E-cadherin repression and metastasis in hepatocellular carcinoma," *Cancer Science*, vol. 110, no. 11, pp. 3442–3452, 2019.
 - [72] M. Gu, T. B. Toh, L. Hooi, J. J. Lim, X. Zhang, and E. K. H. Chow, "Nanodiamond-mediated delivery of a G9a inhibitor for hepatocellular carcinoma therapy," *ACS Applied Materials & Interfaces*, vol. 11, no. 49, pp. 45427–45441, 2019.
 - [73] C. Zhang, C. Yang, M. J. Feldman et al., "Vorinostat suppresses hypoxia signaling by modulating nuclear translocation of hypoxia inducible factor 1 alpha," *Oncotarget*, vol. 8, no. 34, pp. 56110–56125, 2017.
 - [74] R. Buurman, M. Sandbothe, B. Schlegelberger, and B. Skawran, "HDAC inhibition activates the apoptosome via Apaf1 upregulation in hepatocellular carcinoma," *European Journal of Medical Research*, vol. 21, no. 1, p. 26, 2016.
 - [75] S. Bhattacharya, D. Reddy, A. Ingle, B. Khade, and S. Gupta, "Brief Communication: Featured Article: Histone H2A mono-ubiquitination and cellular transformation are inversely related in N-nitrosodiethylamine-induced hepatocellular carcinoma," *Experimental Biology and Medicine*, vol. 241, no. 16, pp. 1739–1744, 2016.
 - [76] P. Kotantaki and G. Mosialos, "The expression of tumor suppressor gene p53 upregulated by histone deacetylase inhibitors in human hepatocellular carcinoma cell lines," *Cell Biochemistry and Function*, vol. 34, no. 7, pp. 465–468, 2016.
 - [77] S. Shin, M. Kim, S.-J. Lee, K.-S. Park, and C. H. Lee, "Trichostatin A sensitizes hepatocellular carcinoma cells to enhanced NK cell-mediated killing by regulating immune-related genes," *Cancer Genomics & Proteomics*, vol. 14, no. 5, pp. 349–362, 2017.
 - [78] T. Chen, C. Gu, C. Xue et al., "LncRNA-uc002mbe.2 interacting with hnRNP A2B1 mediates AKT deactivation and p21 up-regulation induced by trichostatin in liver cancer cells," *Frontiers in Pharmacology*, vol. 8, p. 669, 2017.
 - [79] J. C. Chen, H. Y. Chuang, Y. J. Liao et al., "Enhanced cytotoxicity of human hepatocellular carcinoma cells following pretreatment with sorafenib combined with trichostatin A," *Oncology Letters*, vol. 17, no. 1, pp. 638–645, 2018.
 - [80] M. Fu, W. Shi, Z. Li, and H. Liu, "Activation of mPTP-dependent mitochondrial apoptosis pathway by a novel pan HDAC inhibitor resminostat in hepatocellular carcinoma cells," *Biochemical and Biophysical Research Communications*, vol. 477, no. 4, pp. 527–533, 2016.
 - [81] X. Peng, D. Zhang, Z. Li, M. Fu, and H. Liu, "mTOR inhibition sensitizes human hepatocellular carcinoma cells to resminostat," *Biochemical and Biophysical Research Communications*, vol. 477, no. 4, pp. 556–562, 2016.
 - [82] J. Soukupova, E. Bertran, I. Peñuelas-Haro et al., "Resminostat induces changes in epithelial plasticity of hepatocellular carcinoma cells and sensitizes them to sorafenib-induced apoptosis," *Oncotarget*, vol. 8, no. 66, pp. 110367–110379, 2017.
 - [83] M. Bitzer, M. Horger, E. G. Giannini et al., "Resminostat plus sorafenib as second-line therapy of advanced hepatocellular carcinoma – the SHELTER study," *Journal of Hepatology*, vol. 65, no. 2, pp. 280–288, 2016.
 - [84] W. Y. Tak, B.-Y. Ryoo, H. Y. Lim et al., "Phase I/II study of first-line combination therapy with sorafenib plus resminostat, an oral HDAC inhibitor, versus sorafenib monotherapy for advanced hepatocellular carcinoma in east Asian patients," *Investigational New Drugs*, vol. 36, no. 6, pp. 1072–1084, 2018.
 - [85] S. Zopf, M. Ocker, D. Neureiter et al., "Inhibition of DNA methyltransferase activity and expression by treatment with the pan-deacetylase inhibitor panobinostat in hepatocellular carcinoma cell lines," *BMC Cancer*, vol. 12, no. 1, p. 386, 2012.
 - [86] P. Di Fazio, P. Waldegger, S. Jabari et al., "Autophagy-related cell death by pan-histone deacetylase inhibition in liver cancer," *Oncotarget*, vol. 7, no. 20, pp. 28998–29010, 2016.
 - [87] S. Maschauer, S. Gahr, M. Gandesiri et al., "In vivo monitoring of the anti-angiogenic therapeutic effect of the pan-deacetylase inhibitor panobinostat by small animal PET in a mouse model of gastrointestinal cancers," *Nuclear Medicine and Biology*, vol. 43, no. 1, pp. 27–34, 2016.
 - [88] B. Liao, Y. Zhang, Q. Sun, and P. Jiang, "Vorinostat enhances the anticancer effect of oxaliplatin on hepatocellular carcinoma cells," *Cancer Medicine*, vol. 7, no. 1, pp. 196–207, 2018.

- [89] H. Park, I. Garrido-Laguna, A. Naing et al., "Phase I dose-escalation study of the mTOR inhibitor sirolimus and the HDAC inhibitor vorinostat in patients with advanced malignancy," *Oncotarget*, vol. 7, no. 41, pp. 67521–67531, 2016.
- [90] D. Llopiz, M. Ruiz, L. Villanueva et al., "Enhanced anti-tumor efficacy of checkpoint inhibitors in combination with the histone deacetylase inhibitor belinostat in a murine hepatocellular carcinoma model," *Cancer Immunology, Immunotherapy*, vol. 68, no. 3, pp. 379–393, 2019.
- [91] S. Zheng, S. Guo, Q. Zhong et al., "Biocompatible boron-containing prodrugs of belinostat for the Potential Treatment of Solid Tumors," *ACS Medicinal Chemistry Letters*, vol. 9, no. 2, pp. 149–154, 2018.
- [92] M. Sanaei, F. Kavooosi, A. Roustazadeh, and H. Shahsavani, "In vitro effect of the histone deacetylase inhibitor valproic acid on viability and apoptosis of the PLC/PRF5 human hepatocellular carcinoma cell line," *Asian Pacific Journal of Cancer Prevention*, vol. 19, no. 9, pp. 2507–2510, 2018.
- [93] J. Aucamp, H. C. Van Dyk, A. J. Bronkhorst, and P. J. Pretorius, "Valproic acid alters the content and function of the cell-free DNA released by hepatocellular carcinoma (HepG2) cells in vitro," *Biochimie*, vol. 140, pp. 93–105, 2017.
- [94] J. I. Yu, C. Choi, S. W. Shin et al., "Valproic acid sensitizes hepatocellular carcinoma cells to proton therapy by suppressing NRF2 activation," *Scientific Reports*, vol. 7, no. 1, article 14986, 2017.
- [95] S. K. Saha, Y. Yin, K. Kim et al., "Valproic acid induces endocytosis-mediated doxorubicin internalization and shows synergistic cytotoxic effects in hepatocellular carcinoma cells," *International Journal of Molecular Sciences*, vol. 18, no. 5, p. 1048, 2017.
- [96] W. Zhu, Q. Liang, X. Yang, Y. Yu, X. Shen, and G. Sun, "Combination of sorafenib and valproic acid synergistically induces cell apoptosis and inhibits hepatocellular carcinoma growth via down-regulating Notch3 and pAkt," *American Journal of Cancer Research*, vol. 7, no. 12, pp. 2503–2514, 2017.
- [97] D. H. Lee, J. Y. Nam, Y. Chang et al., "Synergistic effect of cytokine-induced killer cell with valproate inhibits growth of hepatocellular carcinoma cell in a mouse model," *Cancer Biology & Therapy*, vol. 18, no. 1, pp. 67–75, 2016.
- [98] M. Sanaei, F. Kavooosi, and H. Behjoo, "Effect of valproic acid and zebularine on SOCS-1 and SOCS-3 gene expression in colon carcinoma SW48 cell line," *Experimental Oncology*, vol. 42, no. 3, 2020.
- [99] K. Pant, A. Saraya, and S. K. Venugopal, "Oxidative stress plays a key role in butyrate-mediated autophagy via Akt/mTOR pathway in hepatoma cells," *Chemico-Biological Interactions*, vol. 273, pp. 99–106, 2017.
- [100] L.-A. Macfarlane and P. R. Murphy, "MicroRNA: biogenesis, function and role in cancer," *Current Genomics*, vol. 11, no. 7, pp. 537–561, 2010.
- [101] J. O'Brien, H. Hayder, Y. Zayed, and C. Peng, "Overview of microRNA biogenesis, mechanisms of actions, and circulation," *Frontiers in Endocrinology*, vol. 9, p. 402, 2018.
- [102] M.-H. Hu, C.-Y. Ma, X.-M. Wang et al., "MicroRNA-126 inhibits tumor proliferation and angiogenesis of hepatocellular carcinoma by down-regulating EGFL7 expression," *Oncotarget*, vol. 7, no. 41, pp. 66922–66934, 2016.
- [103] B.-Q. Jing, Y. Ou, L. Zhao, Q. Xie, and Y.-X. Zhang, "Experimental study on the prevention of liver cancer angiogenesis via miR-126," *European Review for Medical and Pharmacological Sciences*, vol. 21, no. 22, pp. 5096–5100, 2017.
- [104] C. Du, Z. Lv, L. Cao et al., "MiR-126-3p suppresses tumor metastasis and angiogenesis of hepatocellular carcinoma by targeting LRP6 and PIK3R2," *Journal of Translational Medicine*, vol. 12, no. 1, p. 259, 2014.
- [105] C. Zhao, Y. Li, M. Zhang, Y. Yang, and L. Chang, "miR-126 inhibits cell proliferation and induces cell apoptosis of hepatocellular carcinoma cells partially by targeting Sox2," *Human Cell*, vol. 28, no. 2, pp. 91–99, 2015.
- [106] L. Xiang, H. Ou, X. Liu et al., "Loss of tumor suppressor miR-126 contributes to the development of hepatitis B virus-related hepatocellular carcinoma metastasis through the upregulation of ADAM9," *Tumor Biology*, vol. 39, no. 6, p. 101042831770912, 2017.
- [107] H. Chen, R. Miao, J. Fan et al., "Decreased expression of miR-126 correlates with metastatic recurrence of hepatocellular carcinoma," *Clinical & Experimental Metastasis*, vol. 30, no. 5, pp. 651–658, 2013.
- [108] K. R. Babu and M. U. Muckenthaler, "miR-148a regulates expression of the transferrin receptor 1 in hepatocellular carcinoma," *Scientific Reports*, vol. 9, no. 1, article 1518, 2019.
- [109] X. Chen, L. Bo, W. Lu, G. Zhou, and Q. Chen, "MicroRNA-148b targets Rho-associated protein kinase 1 to inhibit cell proliferation, migration and invasion in hepatocellular carcinoma," *Molecular Medicine Reports*, vol. 13, no. 1, pp. 477–482, 2016.
- [110] K. H. Jung, J. Zhang, C. Zhou et al., "Differentiation therapy for hepatocellular carcinoma: multifaceted effects of miR-148a on tumor growth and phenotype and liver fibrosis," *Hepatology*, vol. 63, no. 3, pp. 864–879, 2016.
- [111] J.-P. Zhang, C. Zeng, L. Xu, J. Gong, J.-H. Fang, and S.-M. Zhuang, "MicroRNA-148a suppresses the epithelial-mesenchymal transition and metastasis of hepatoma cells by targeting Met/Snail signaling," *Oncogene*, vol. 33, no. 31, pp. 4069–4076, 2014.
- [112] X.-Y. Liu, Y.-J. He, Q.-H. Yang et al., "Induction of autophagy and apoptosis by miR-148a through the sonic hedgehog signaling pathway in hepatic stellate cells," *American Journal of Cancer Research*, vol. 5, no. 9, pp. 2569–2589, 2015.
- [113] X.-R. Long, Y. He, C. Huang, and L. Jun, "MicroRNA-148a is silenced by hypermethylation and interacts with DNA methyltransferase 1 in hepatocellular carcinogenesis," *International Journal of Oncology*, vol. 44, no. 6, pp. 1915–1922, 2014.
- [114] E. Callegari, L. D'Abundo, P. Guerriero et al., "miR-199a-3p modulates MTOR and PAK4 pathways and inhibits tumor growth in a hepatocellular carcinoma transgenic mouse model," *Molecular Therapy-Nucleic Acids*, vol. 11, pp. 485–493, 2018.
- [115] A. Varshney, J. J. Panda, A. K. Singh et al., "Targeted delivery of microRNA-199a-3p using self-assembled dipeptide nanoparticles efficiently reduces hepatocellular carcinoma in mice," *Hepatology*, vol. 67, no. 4, pp. 1392–1407, 2018.
- [116] J. Guan, Z. Liu, M. Xiao et al., "MicroRNA-199a-3p inhibits tumorigenesis of hepatocellular carcinoma cells by targeting ZHX1/PUMA signal," *American Journal of Translational Research*, vol. 9, no. 5, pp. 2457–2465, 2017.
- [117] C. Giovannini, F. Fornari, R. Dallo et al., "MiR-199-3p replacement affects E-cadherin expression through Notch1 targeting in hepatocellular carcinoma," *Acta Histochemica*, vol. 120, no. 2, pp. 95–102, 2018.

- [118] C. Xiao, X. Wan, H. Yu et al., "LncRNA-AB209371 promotes the epithelial-mesenchymal transition of hepatocellular carcinoma cells," *Oncology Reports*, vol. 41, no. 5, pp. 2957–2966, 2019.
- [119] G. Huang, H. Shan, D. Li, B. Zhou, and P. Pang, "MiR-199a-5p suppresses tumorigenesis by targeting clathrin heavy chain in hepatocellular carcinoma," *Cell Biochemistry and Function*, vol. 35, no. 2, pp. 98–104, 2017.
- [120] R. Gui, R. Huang, J.-H. Zhang, X.-H. Wen, and X.-M. Nie, "MicroRNA-199a-5p inhibits VEGF-induced tumorigenesis through targeting oxidoreductase domain-containing protein 1 in human HepG2 cells," *Oncology Reports*, vol. 35, no. 4, pp. 2216–2222, 2016.
- [121] S.-P. Jiang and Z.-R. Li, "MiR-503-5p regulates cell epithelial-to-mesenchymal transition, metastasis and prognosis of hepatocellular carcinoma through inhibiting WEE1," *European Review for Medical and Pharmacological Sciences*, vol. 23, no. 5, pp. 2028–2037, 2019.
- [122] B. Li, L. Liu, X. Li, and L. Wu, "miR-503 suppresses metastasis of hepatocellular carcinoma cell by targeting PRMT1," *Biochemical and Biophysical Research Communications*, vol. 464, no. 4, pp. 982–987, 2015.
- [123] J. Zhou, Y. Tao, C. Peng, P. Gu, and W. Wang, "miR-503 regulates metastatic function through Rho guanine nucleotide exchanger factor 19 in hepatocellular carcinoma," *The Journal of Surgical Research*, vol. 188, no. 1, pp. 129–136, 2014.
- [124] X. Yang, J. Zang, X. Pan et al., "miR-503 inhibits proliferation making human hepatocellular carcinoma cells susceptible to 5-fluorouracil by targeting EIF4E," *Oncology Reports*, vol. 37, no. 1, pp. 563–570, 2017.
- [125] Y. Xiao, Q. Tian, J. He, M. Huang, C. Yang, and L. Gong, "MiR-503 inhibits hepatocellular carcinoma cell growth via inhibition of insulin-like growth factor 1 receptor," *Oncotargets and Therapy*, vol. 9, pp. 3535–3544, 2016.
- [126] Y. Liu, J. Tan, S. Ou, J. Chen, and L. Chen, "MicroRNA-101-3p suppresses proliferation and migration in hepatocellular carcinoma by targeting the HGF/c-Met pathway," *Investigational New Drugs*, vol. 38, no. 1, pp. 60–69, 2020.
- [127] W. Si, Y. Zhao, J. Zhou, Q. Zhang, and Y. Zhang, "The coordination between ZNF217 and LSD1 contributes to hepatocellular carcinoma progress and is negatively regulated by miR-101," *Experimental Cell Research*, vol. 379, no. 1, pp. 1–10, 2019.
- [128] J. Yang, Y. Lu, Y.-Y. Lin et al., "Vascular mimicry formation is promoted by paracrine TGF- β and SDF1 of cancer-associated fibroblasts and inhibited by miR-101 in hepatocellular carcinoma," *Cancer Letters*, vol. 383, no. 1, pp. 18–27, 2016.
- [129] X. Chen and N. Zhang, "Downregulation of lncRNA NEAT1_2 radiosensitizes hepatocellular carcinoma cells through regulation of miR-101-3p/WEE1 axis," *Cell Biology International*, vol. 43, no. 1, pp. 44–55, 2019.
- [130] Y. Lei, Q. Wang, L. Shen, Y. Tao, and C. Liu, "MicroRNA-101 suppresses liver fibrosis by downregulating PI3K/Akt/mTOR signaling pathway," *Clinics and Research in Hepatology and Gastroenterology*, vol. 43, no. 5, pp. 575–584, 2019.
- [131] F. Xu, J.-Z. Liao, G.-Y. Xiang et al., "MiR-101 and doxorubicin codelivered by liposomes suppressing malignant properties of hepatocellular carcinoma," *Cancer Medicine*, vol. 6, no. 3, pp. 651–661, 2017.
- [132] S. Yan, X. Shan, K. Chen et al., "LINC00052/miR-101-3p axis inhibits cell proliferation and metastasis by targeting SOX9 in hepatocellular carcinoma," *Gene*, vol. 679, pp. 138–149, 2018.
- [133] R. Hari and S. Parthasarathy, "Prediction of coding and non-coding RNA," in *Encyclopedia of Bioinformatics and Computational Biology*, pp. 230–240, Elsevier, 2019.
- [134] L. Peng, X. Q. Yuan, C. Y. Zhang et al., "The emergence of long non-coding RNAs in hepatocellular carcinoma: an update," *Journal of Cancer*, vol. 9, no. 14, pp. 2549–2558, 2018.
- [135] Z. S. Niu, X. J. Niu, and W. H. Wang, "Long non-coding RNAs in hepatocellular carcinoma: potential roles and clinical implications," *World Journal of Gastroenterology*, vol. 23, no. 32, pp. 5860–5874, 2017.
- [136] X. Hu, J. Jiang, Q. Xu, C. Ni, L. Yang, and D. Huang, "A systematic review of long noncoding RNAs in hepatocellular carcinoma: molecular mechanism and clinical implications," *BioMed Research International*, vol. 2018, 13 pages, 2018.
- [137] L. Zhang, J. Hu, M. Hao, and L. Bu, "Long noncoding RNA Linc01296 promotes hepatocellular carcinoma development through regulation of the miR-26a/PTEN axis," *Biological Chemistry*, vol. 401, no. 3, pp. 407–416, 2020.
- [138] L. Fang, J. Sun, Z. Pan et al., "Long non-coding RNA NEAT1 promotes hepatocellular carcinoma cell proliferation through the regulation of miR-129-5p-VCP-I κ B," *American Journal of Physiology-Gastrointestinal and Liver Physiology*, vol. 313, no. 2, pp. G150–G156, 2017.
- [139] N. Zhang and X. Chen, "Long non-coding RNA LINC00346 promotes hepatocellular carcinoma progression through the Wnt/ β -catenin signaling pathway," *SSRN Electronic Journal*, 2019.
- [140] K. Cai, T. Li, L. Guo et al., "Long non-coding RNA LINC00467 regulates hepatocellular carcinoma progression by modulating miR-9-5p/PPARA expression," *Open Biology*, vol. 9, no. 9, p. 190074, 2019.
- [141] H. Wang, L. Liang, Q. Dong et al., "Long noncoding RNA miR503HG, a prognostic indicator, inhibits tumor metastasis by regulating the HNRNPA2B1/NF- κ B pathway in hepatocellular carcinoma," *Theranostics*, vol. 8, no. 10, pp. 2814–2829, 2018.
- [142] Y. Wei, Z. Wang, Y. Zong, D. Deng, P. Chen, and J. Lu, "LncRNA MFI2-AS1 promotes HCC progression and metastasis by acting as a competing endogenous RNA of miR-134 to upregulate FOXM1 expression," *Biomedicine & Pharmacotherapy*, vol. 125, article 109890, 2020.
- [143] Z. Zhang, L. Yang, X. Yao, M. Yang, and G. Li, "LncRNA-ZNF281 interacts with miR-539 to promote hepatocellular carcinoma cell invasion and migration," *Cancer Biotherapy & Radiopharmaceuticals*, vol. 35, no. 2, pp. 137–142, 2020.
- [144] W. Zhang, Y. Liu, Y. Fu et al., "Long non-coding RNA LINC00160 functions as a decoy of microRNA-132 to mediate autophagy and drug resistance in hepatocellular carcinoma via inhibition of PIK3R3," *Cancer Letters*, vol. 478, pp. 22–33, 2020.
- [145] L. H. Luo, M. Jin, L. Q. Wang et al., "Long noncoding RNA TCL6 binds to miR-106a-5p to regulate hepatocellular carcinoma cells through PI3K/AKT signaling pathway," *Journal of Cellular Physiology*, vol. 235, no. 9, pp. 6154–6166, 2020.
- [146] S. Wu, S. Chen, N. Lin, and J. Yang, "Long non-coding RNA SUMO1P3 promotes hepatocellular carcinoma progression through activating Wnt/ β -catenin signalling pathway by targeting miR-320a," *Journal of Cellular and Molecular Medicine*, vol. 24, no. 5, pp. 3108–3116, 2020.

- [147] F. Wei, L. Yang, D. Jiang et al., "Long noncoding RNA DUXAP8 contributes to the progression of hepatocellular carcinoma via regulating miR-422a/PDK2 axis," *Cancer Medicine*, vol. 9, no. 7, pp. 2480–2490, 2020.
- [148] L. Sun, L. Wang, T. Chen et al., "LncRNA RUNX1-IT1 which is downregulated by hypoxia-driven histone deacetylase 3 represses proliferation and cancer stem-like properties in hepatocellular carcinoma cells," *Cell Death & Disease*, vol. 11, no. 2, pp. 1–5, 2020.
- [149] A. Qu and Q. Yang, "LncRNA SNHG1 promotes cell progression and metastasis via sponging miR-377-3p in hepatocellular carcinoma," *Neoplasia*, vol. 67, no. 3, pp. 557–566, 2020.
- [150] H. L. Zhu, R. Yuan, H. Wang, C. Li, and J. Wei, "LncRNA MINCR promotes the development of liver cancer by regulating microRNA-107/ β -catenin," *Journal of BU ON*, vol. 25, no. 2, pp. 972–980, 2020.
- [151] Z. Wen, L. Lian, H. Ding et al., "LncRNA ANCR promotes hepatocellular carcinoma metastasis through upregulating HNRNPA1 expression," *RNA Biology*, vol. 17, no. 3, pp. 381–394, 2020.
- [152] J. T. Zhao, B. J. Chi, Y. Sun et al., "LINC00174 is an oncogenic lncRNA of hepatocellular carcinoma and regulates miR-320/S100A10 axis," *Cell Biochemistry and Function*, vol. 38, no. 7, pp. 859–869, 2020.
- [153] H. Wang, Q. Guo, K. B. Nampoukime, P. Yang, and K. Ma, "Long non-coding RNA LINC00467 drives hepatocellular carcinoma progression via inhibiting NR4A3," *Journal of Cellular and Molecular Medicine*, vol. 24, no. 7, pp. 3822–3836, 2020.
- [154] L. H. Mao, S. Y. Chen, X. Q. Li et al., "LncRNA-LALR1 upregulates small nucleolar RNA SNORD72 to promote growth and invasion of hepatocellular carcinoma," *Aging*, vol. 12, no. 5, pp. 4527–4546, 2020.
- [155] H. Q. Bi, Z. H. Li, and H. Zhang, "Long noncoding RNA HAND2-AS1 reduced the viability of hepatocellular carcinoma via targeting microRNA-300/SOCS5 axis," *Hepatobiliary & Pancreatic Diseases International*, 2020.
- [156] Y. Chi, Z. Gong, H. Xin, Z. Wang, and Z. Liu, "Long noncoding RNA lncARSR promotes nonalcoholic fatty liver disease and hepatocellular carcinoma by promoting YAP1 and activating the IRS2/AKT pathway," *Journal of Translational Medicine*, vol. 18, no. 1, p. 126, 2020.
- [157] W. Pan, N. Zhang, W. Liu et al., "The long noncoding RNAGAS8-AS1 suppresses hepatocarcinogenesis by epigenetically activating the tumor suppressor GAS8," *The Journal of Biological Chemistry*, vol. 293, no. 44, pp. 17154–17165, 2018.
- [158] R. Shang, M. Wang, B. Dai et al., "Long noncoding RNASLC2A1-AS1 regulates aerobic glycolysis and progression in hepatocellular carcinoma via inhibiting the STAT3/FOXO1/FOXO3 pathway," *Molecular Oncology*, vol. 14, no. 6, pp. 1381–1396, 2020.
- [159] C. Liu, M. Zhang, J. Zhao et al., "LncRNA FOXD3-AS1 mediates AKT pathway to promote growth and invasion in hepatocellular carcinoma through regulating RICTOR," *Cancer Biotherapy & Radiopharmaceuticals*, vol. 35, no. 4, pp. 292–300, 2020.
- [160] P. A. Hu, Y. Y. Miao, S. Yu, and N. Guo, "Long non-coding RNA SNHG5 promotes human hepatocellular carcinoma progression by regulating miR-363-3p/RNF38 axis," *European Review for Medical and Pharmacological Sciences*, vol. 24, no. 7, pp. 3592–3604, 2020.
- [161] W. Xuan, C. Zhou, and G. You, "LncRNA LINC00668 promotes cell proliferation, migration, invasion ability and EMT process in hepatocellular carcinoma by targeting miR-532-5p/YY1 axis," *Bioscience Reports*, vol. 40, no. 5, 2020.
- [162] J. Gao, C. Dai, X. Yu, X. B. Yin, and F. Zhou, "LncRNA LEF1-AS1 silencing diminishes EZH2 expression to delay hepatocellular carcinoma development by impairing CEBPB-interaction with CDCA7," *Cell Cycle*, vol. 19, no. 8, pp. 870–883, 2020.
- [163] C. Shi, Q. Yang, S. Pan et al., "LncRNA OIP5-AS1 promotes cell proliferation and migration and induces angiogenesis via regulating miR-3163/VEGFA in hepatocellular carcinoma," *Cancer Biology & Therapy*, vol. 21, no. 7, pp. 604–614, 2020.
- [164] W. J. Huang, X. P. Tian, S. X. Bi et al., "The β -catenin/TCF-4-LINC01278-miR-1258-Smad2/3 axis promotes hepatocellular carcinoma metastasis," *Oncogene*, vol. 39, no. 23, pp. 4538–4550, 2020.
- [165] W. Zhang, L. Han, P. Xing et al., "LncRNA RHPN1-AS1 accelerates proliferation, migration, and invasion via regulating miR-485-5p/BSG axis in hepatocellular carcinoma," *Nannyn-Schmiedeberg's Archives of Pharmacology*, vol. 21, pp. 1–9, 2020.
- [166] X. Guo and Y. Wang, "LncRNA TMPO-AS1 promotes hepatocellular carcinoma cell proliferation, migration and invasion through sponging miR-329-3p to stimulate FOXK1-mediated AKT/mTOR signaling pathway," *Cancer Medicine*, vol. 9, no. 14, pp. 5235–5246, 2020.
- [167] Y. Liang, D. Zhang, T. Zheng et al., "LncRNA-SOX2OT promotes hepatocellular carcinoma invasion and metastasis through miR-122-5p-mediated activation of PKM2," *Oncogene*, vol. 9, no. 5, pp. 1–2, 2020.
- [168] B. Wang, J. Xian, J. Zang et al., "Long non-coding RNA FENDRR inhibits proliferation and invasion of hepatocellular carcinoma by down-regulating glypican-3 expression," *Biochemical and Biophysical Research Communications*, vol. 509, no. 1, pp. 143–147, 2019.
- [169] M. M. Wu, W. D. Shen, C. W. Zou, H. J. Chen, and H. M. Guo, "LncRNA-HEIH suppresses hepatocellular carcinoma cell growth and metastasis by up-regulating miR-199a-3p," *European Review for Medical and Pharmacological Sciences*, vol. 24, no. 11, pp. 6031–6038, 2020.
- [170] J. H. Wu, K. Xu, J. H. Liu et al., "LncRNA MT1JP inhibits the malignant progression of hepatocellular carcinoma through regulating AKT," *European Review for Medical and Pharmacological Sciences*, vol. 24, no. 12, pp. 6647–6656, 2020.
- [171] Y. S. Ma, K. J. Chu, C. C. Ling, T. M. Wu, and X. C. Zhu, "Long noncoding RNA OIP5-AS1 promotes the progression of liver hepatocellular carcinoma via regulating the hsa-miR-26a-3p/EPHA2 axis," *Molecular Therapy–Nucleic Acids*, vol. 21, pp. 229–241, 2020.
- [172] C. Cao, Q. Zhong, L. Lu et al., "Long noncoding RNA MSC-AS1 promotes hepatocellular carcinoma oncogenesis via inducing the expression of phosphoglycerate kinase 1," *Cancer Medicine*, vol. 9, no. 14, pp. 5174–5184, 2020.
- [173] G. Zhang, X. Chen, L. Ma et al., "LINC01419 facilitates hepatocellular carcinoma growth and metastasis through targeting EZH2-regulated RECK," *Aging*, vol. 12, no. 11, pp. 11071–11084, 2020.
- [174] W. Hu, H. Feng, X. Xu et al., "Long noncoding RNA FOXD2-AS1 aggravates hepatocellular carcinoma tumorigenesis by regulating the miR-206/MAP3K1 axis," *Cancer Medicine*, vol. 9, no. 15, pp. 5620–5631, 2020.

- [175] W. Li, J. Ge, J. Xie, J. Yang, J. Chen, and T. He, "LncRNA-TUG1 promotes hepatocellular carcinoma migration and invasion via targeting miR-137/AKT2 axis," *Cancer Biotherapy & Radiopharmaceuticals*, 2020.
- [176] S. J. Tang and J. B. Yang, "LncRNA SNHG14 aggravates invasion and migration as ceRNA via regulating miR-656-3p/SIRT5 pathway in hepatocellular carcinoma," *Molecular and Cellular Biochemistry*, vol. 473, no. 1–2, pp. 143–153, 2020.
- [177] Y. Xu, Y. Liu, Z. Li et al., "Long non-coding RNA H19 is involved in sorafenib resistance in hepatocellular carcinoma by upregulating miR-675," *Oncology Reports*, vol. 44, no. 1, pp. 165–173, 2020.
- [178] H. Topel, E. Bagirsakci, D. Comez, G. Bagci, G. Cakan-Akdogan, and N. Atabay, "LncRNA HOTAIR overexpression induced downregulation of c-Met signaling promotes hybrid epithelial/mesenchymal phenotype in hepatocellular carcinoma cells," *Cell Communication and Signaling: CCS*, vol. 18, no. 1, p. 110, 2020.
- [179] Y. Pan, T. Qin, S. Yin, X. Zhang, X. Gao, and L. Mu, "Long non-coding RNA UC001kfo promotes hepatocellular carcinoma proliferation and metastasis by targeting α -SMA," *Bio-medicine & Pharmacotherapy*, vol. 87, pp. 669–677, 2017.
- [180] Y. Zou, Z. Sun, and S. Sun, "LncRNA HCG18 contributes to the progression of hepatocellular carcinoma via miR-214-3p/CENPM axis," *Journal of Biochemistry*, vol. 168, no. 5, 2020.
- [181] S. Kong, H. Xue, Y. Li et al., "The long noncoding RNA OTUD6B-AS1 enhances cell proliferation and the invasion of hepatocellular carcinoma cells through modulating GSKIP/Wnt/ β -catenin signalling via the sequestration of miR-664b-3p," *Experimental Cell Research*, vol. 395, no. 1, p. 112180, 2020.
- [182] C. Sun, S. Huang, Y. Hou et al., "Long noncoding RNA AC092171.4 promotes hepatocellular carcinoma progression by sponging microRNA-1271 and upregulating GRB2," *Aging*, vol. 12, no. 14, pp. 14141–14156, 2020.
- [183] X. Qian, S. Li, Z. Yang, and J. Zhang, "The long non-coding RNA HLNC1 potentiates hepatocellular carcinoma progression via interaction with USP49," *Journal of Clinical Laboratory Analysis*, vol. 34, no. 11, 2020.
- [184] Y. Duan, J. Chen, Y. Yang, Z. Qu, Y. Lu, and D. Sun, "LncRNA HOTAIR contributes Taxol-resistance of hepatocellular carcinoma cells via activating AKT phosphorylation by down-regulating miR-34a," *Bioscience Reports*, vol. 40, no. 7, 2020.
- [185] Y. A. Chen, L. Cheng, Y. Zhang, L. Peng, and H. G. Yang, "LncRNA RUSC1-AS1 promotes the proliferation of hepatocellular carcinoma cells through modulating NOTCH signaling," *Neoplasia*, 2020.
- [186] Y. Z. Lun, Z. P. Pan, S. A. Liu et al., "The peptide encoded by a novel putative lncRNA HBVPTAP inducing the apoptosis of hepatocellular carcinoma cells by modulating JAK/STAT signaling pathways," *Virus Research*, vol. 287, p. 198104, 2020.
- [187] H. Zhang, H. B. Xu, E. Kurban, and H. W. Luo, "LncRNA SNHG14 promotes hepatocellular carcinoma progression via H3K27 acetylation activated PABPC1 by PTEN signaling," *Cell Death & Disease*, vol. 11, no. 8, pp. 1–3, 2020.
- [188] X. Wang, M. L. Cheng, Y. Gong, W. J. Ma, B. Li, and Y. Z. Jiang, "LncRNA DANCR promotes ATG7 expression to accelerate hepatocellular carcinoma cell proliferation and autophagy by sponging miR-222-3p," *European Review for Medical and Pharmacological Sciences*, vol. 24, no. 17, pp. 8778–8787, 2020.
- [189] Z. Liu, H. Mo, L. Sun et al., "Long noncoding RNA PICSAR/miR-588/EIF6 axis regulates tumorigenesis of hepatocellular carcinoma by activating PI3K/AKT/mTOR signaling pathway," *Cancer Science*, vol. 111, no. 11, pp. 4118–4128, 2020.
- [190] X. Xu, Y. Lou, J. Tang et al., "The long non-coding RNA Linc-GALH promotes hepatocellular carcinoma metastasis via epigenetically regulating Gankyrin," *Cell Death & Disease*, vol. 10, no. 2, p. 86, 2019.
- [191] Y. Liu, W. Yan, D. Zhou, G. Jin, and X. Cheng, "Long non-coding RNA HOXA11-AS accelerates cell proliferation and epithelial-mesenchymal transition in hepatocellular carcinoma by modulating the miR-506-3p/Slug axis," *International Journal of Molecular Medicine*, vol. 46, no. 5, pp. 1805–1815, 2020.
- [192] Z. Wu, Z. H. Wei, and S. H. Chen, "LncUBE2R2-AS1 acts as a microRNA sponge of miR-302b to promote HCC progression via activation EGFR-PI3K-AKT signaling pathway," *Cell Cycle*, vol. 19, no. 19, pp. 2426–2435, 2020.
- [193] H. He, Y. Wang, P. Ye et al., "Long noncoding RNA ZFPM2-AS1 acts as a miRNA sponge and promotes cell invasion through regulation of miR-139/GDF10 in hepatocellular carcinoma," *Journal of Experimental & Clinical Cancer Research*, vol. 39, no. 1, p. 159, 2020.
- [194] J. Gao, C. Dai, X. Yu, X. Yin, and F. Zhou, "Long noncoding RNA LEF1-AS1 acts as a microRNA-10a-5p regulator to enhance MSI1 expression and promote chemoresistance in hepatocellular carcinoma cells through activating AKT signaling pathway," *Journal of Cellular Biochemistry*, vol. 12, 2020.
- [195] Y. Li, D. Guo, G. Lu et al., "LncRNA SNAI3-AS1 promotes PEG10-mediated proliferation and metastasis via decoying of miR-27a-3p and miR-34a-5p in hepatocellular carcinoma," *Cell Death & Disease*, vol. 11, no. 8, 2020.
- [196] C. Wang, H. Zi, Y. Wang, B. Li, Z. Ge, and X. Ren, "Retracted article: LncRNACASC15 promotes tumour progression through SOX4/Wnt/ β -catenin signalling pathway in hepatocellular carcinoma," *Artificial Cells, Nanomedicine, and Biotechnology*, vol. 48, no. 1, pp. 763–769, 2020.
- [197] J. Zhang, X. Zhao, X. Ma, Z. Yuan, and M. Hu, "KCNQ1OT1 contributes to sorafenib resistance and programmed death-ligand-1-mediated immune escape via sponging miR-506 in hepatocellular carcinoma cells," *International Journal of Molecular Medicine*, vol. 46, no. 5, pp. 1794–1804, 2020.
- [198] L. Lxia, B. Liu, J. Yu, Z. Dyun, S. Jhong, and P. Liang, "SP1-induced upregulation of lncRNA CTBP1-AS2 accelerates the hepatocellular carcinoma tumorigenesis through targeting CEP55 via sponging miR-195-5p," *Biochemical and Biophysical Research Communications*, 2020.
- [199] Y. Cao, F. Zhang, H. Wang et al., "LncRNA MALAT1 mediates doxorubicin resistance of hepatocellular carcinoma by regulating miR-3129-5p/Nova1 axis," *Molecular and Cellular Biochemistry*, vol. 1, 2020.
- [200] F. Chen, Y. Wang, Y. Cheng et al., "AC006262.5/miR-7855-5p/BPY2C axis facilitates hepatocellular carcinoma proliferation and migration," *Biochemistry and Cell Biology*, 2020.
- [201] Q. Y. Li, K. Yang, F. G. Liu et al., "Long noncoding RNA CASC2c inhibited cell proliferation in hepatocellular carcinoma by inactivated ERK1/2 and Wnt/ β -catenin signaling

- pathway," *Clinical & Translational Oncology*, vol. 22, no. 3, pp. 302–310, 2020.
- [202] B. W. Chen, Y. Zhou, T. Wei et al., "lncRNA-POIR promotes epithelial–mesenchymal transition and suppresses sorafenib sensitivity simultaneously in hepatocellular carcinoma by sponging miR-182-5p," *Journal of Cellular Biochemistry*, 2020.
- [203] H. Wu, T. T. Liu, Y. M. Feng et al., "Prognostic effect of a novel long noncoding RNA signature and comparison with clinical staging systems for patients with hepatitis B virus-related hepatocellular carcinoma after hepatectomy," *Journal of Digestive Diseases*, 2020.
- [204] T. Wan, J. Zheng, R. Yao, S. Yang, W. Zheng, and P. Zhou, "lncRNA DDX11-AS1 accelerates hepatocellular carcinoma progression via the miR-195-5p/MACC1 pathway," *Annals of Hepatology*, vol. 19, 2020.
- [205] G. Yang, L. Zhou, Q. Xu et al., "lncRNA KCNQ1OT1 inhibits the radiosensitivity and promotes the tumorigenesis of hepatocellular carcinoma via the miR-146a-5p/ACER3 axis," *Cell Cycle*, vol. 19, no. 19, pp. 2519–2529, 2020.
- [206] D. Xu, X. Liu, J. Wu et al., "lncRNA WWOX-AS1 sponges miR-20b-5p in hepatocellular carcinoma and represses its progression by upregulating WWOX," *Cancer Biology & Therapy*, vol. 21, no. 10, pp. 927–936, 2020.
- [207] Y. Li, W. Zhuang, M. Huang, and X. Li, "Long noncoding RNA DDX11-AS1 epigenetically represses LATS2 by interacting with EZH2 and DNMT1 in hepatocellular carcinoma," *Biochemical and Biophysical Research Communications*, vol. 514, no. 4, pp. 1051–1057, 2019.
- [208] T. Yi, T. Wang, Y. Shi et al., "Long noncoding RNA 91H overexpression contributes to the growth and metastasis of HCC by epigenetically positively regulating IGF2 expression," *Liver International*, vol. 40, no. 2, pp. 456–467, 2019.
- [209] H. L. Chang, O. A. Bamodu, J. R. Ong, W. H. Lee, C. T. Yeh, and J. T. Tsai, "Targeting the epigenetic non-coding RNA MALAT1/Wnt signaling axis as a therapeutic approach to suppress stemness and metastasis in hepatocellular carcinoma," *Cell*, vol. 9, no. 4, 2020.
- [210] S. C. Xie, J. Q. Zhang, X. L. Jiang et al., "lncRNA CRNDE facilitates epigenetic suppression of CELF2 and LATS2 to promote proliferation, migration and chemoresistance in hepatocellular carcinoma," *Cell Death & Disease*, vol. 11, no. 8, pp. 1–7, 2020.
- [211] X. Xu, J. Gu, X. Ding et al., "LINC00978 promotes the progression of hepatocellular carcinoma by regulating EZH2-mediated silencing of p21 and E-cadherin expression," *Cell Death & Disease*, vol. 10, no. 10, pp. 1–5, 2019.
- [212] D. Gong, P.-C. Feng, X.-F. Ke et al., "Silencing long non-coding RNA LINC01224 inhibits hepatocellular carcinoma progression via microRNA-330-5p-induced inhibition of CHEK1," *Molecular Therapy-Nucleic Acids*, vol. 19, pp. 482–497, 2020.
- [213] H. L. Zhou, Y. F. Zhou, and Z. T. Feng, "Long noncoding RNA ZFAS1 promotes hepatocellular carcinoma proliferation by epigenetically repressing miR-193a-3p," *European Review for Medical and Pharmacological Sciences*, vol. 23, no. 22, pp. 9840–9847, 2019.
- [214] Y. Ji, H. Sun, H. Liang et al., "Evaluation of lncrna anril potential in hepatic cancer progression," *Journal of Environmental Pathology, Toxicology and Oncology*, vol. 38, no. 2, pp. 119–131, 2019.
- [215] J. Bayo, E. J. Fiore, L. M. Dominguez et al., "A comprehensive study of epigenetic alterations in hepatocellular carcinoma identifies potential therapeutic targets," *Journal of Hepatology*, vol. 71, no. 1, pp. 78–90, 2019.
- [216] C. T. Law, L. Wei, F. H. Tsang et al., "HELLS regulates chromatin remodeling and epigenetic silencing of multiple tumor suppressor genes in human hepatocellular carcinoma," *Hepatology*, vol. 69, no. 5, pp. 2013–2030, 2019.
- [217] Y. Zheng, Q. Huang, Z. Ding et al., "Genome-wide DNA methylation analysis identifies candidate epigenetic markers and drivers of hepatocellular carcinoma," *Briefings in Bioinformatics*, vol. 19, no. 1, 2018.
- [218] J. Lu, T. Tan, L. Zhu, H. Dong, and R. Xian, "Hypomethylation causes MIR21 overexpression in tumors," *Molecular Therapy-Oncolytics*, vol. 18, pp. 47–57, 2020.
- [219] F. Xu, L. Zhang, Y. Xu et al., "Hypermethylation of scand3 and myo1g gene are potential diagnostic biomarkers for hepatocellular carcinoma," *Cancers*, vol. 12, no. 8, pp. 1–15, 2020.
- [220] J. L. Peng, J. Z. Wu, G. J. Li et al., "Association of RASSF1A hypermethylation with risk of HBV/HCV-induced hepatocellular carcinoma: a meta-analysis," *Pathology Research and Practice*, vol. 216, no. 10, article 153099, 2020.
- [221] M. C. Yu, C. W. Lee, C. H. Lin et al., "Differential hypermethylation of the VTRNA2-1 promoter in hepatocellular carcinoma as a prognostic factor: tumor marker prognostic study," *International Journal of Surgery*, vol. 79, pp. 282–289, 2020.
- [222] N. Sun, J. Zhang, C. Zhang, B. Zhao, and A. O. Jiao, "DNMTs inhibitor SGI-1027 induces apoptosis in Huh7 human hepatocellular carcinoma cells," *Oncology Letters*, vol. 16, no. 5, pp. 5799–5806, 2018.
- [223] M. Bárcena-Varela, S. Caruso, S. Llerena et al., "Dual targeting of histone methyltransferase G9a and DNA-methyltransferase 1 for the treatment of experimental hepatocellular carcinoma," *Hepatology*, vol. 69, no. 2, pp. 587–603, 2019.
- [224] D. Carlisi, M. Lauricella, A. D'Anneo et al., "The histone deacetylase inhibitor suberoylanilide hydroxamic acid sensitises human hepatocellular carcinoma cells to TRAIL-induced apoptosis by TRAIL-DISC activation," *European Journal of Cancer*, vol. 45, no. 13, pp. 2425–2438, 2009.
- [225] B. He, L. Dai, X. Zhang et al., "The HDAC inhibitor quisinostat (JNJ-26481585) suppresses hepatocellular carcinoma alone and synergistically in combination with sorafenib by G0/G1 phase arrest and apoptosis induction," *International Journal of Biological Sciences*, vol. 14, no. 13, pp. 1845–1858, 2018.
- [226] W. J. Sun, H. Huang, B. He et al., "Romidepsin induces G2/M phase arrest via Erk/cdc25C/cdc2/cyclinB pathway and apoptosis induction through JNK/c-Jun/caspase3 pathway in hepatocellular carcinoma cells," *Biochemical Pharmacology*, vol. 127, pp. 90–100, 2017.
- [227] J. L. Jilek, Q.-Y. Zhang, M.-J. Tu et al., "Bioengineered Let-7c inhibits orthotopic hepatocellular carcinoma and improves overall survival with minimal immunogenicity," *Molecular Therapy-Nucleic Acids*, vol. 14, pp. 498–508, 2019.
- [228] L. Guo, B. Li, M. Miao, J. Yang, and J. Ji, "MicroRNA-663b targets GAB2 to restrict cell proliferation and invasion in hepatocellular carcinoma," *Molecular Medicine Reports*, vol. 19, no. 4, pp. 2913–2920, 2019.

- [229] C. Yang, M. Yin, G. Xu et al., "Biodegradable polymers as a noncoding miRNA nanocarrier for multiple targeting therapy of human hepatocellular carcinoma," *Advanced Healthcare Materials*, vol. 8, no. 8, p. 1801318, 2019.
- [230] H. Huang, Y. Zhu, and S. Li, "MicroRNA-122 mimic transfection contributes to apoptosis in HepG2 cells," *Molecular Medicine Reports*, vol. 12, no. 5, pp. 6918–6924, 2015.
- [231] Y. Shao, X. Song, W. Jiang et al., "MicroRNA-621 acts as a tumor radiosensitizer by directly targeting SETDB1 in hepatocellular carcinoma," *Molecular Therapy*, vol. 27, no. 2, pp. 355–364, 2019.
- [232] X. Jiang and X. Shen, "Knockdown of miR-299-5p inhibits the progression of hepatocellular carcinoma by targeting SIAH1," *Bulletin du Cancer*, vol. 105, no. 10, pp. 873–883, 2018.
- [233] S. Han, Z. Liu, Y. Wang et al., "MicroRNA-577 inhibits the migration and invasion of hepatocellular carcinoma cells by targeting homeobox A1," *Oncology Reports*, vol. 39, no. 6, pp. 2987–2995, 2018.
- [234] C. Luo, D. Yin, H. Zhan et al., "MicroRNA-501-3p suppresses metastasis and progression of hepatocellular carcinoma through targeting LIN7A," *Cell Death & Disease*, vol. 9, no. 5, p. 535, 2018.
- [235] H. Fu, J. Zhang, T. Pan, S. Ai, L. Tang, and F. Wang, "miR-378a enhances the sensitivity of liver cancer to sorafenib by targeting VEGFR, PDGFR β and c-Raf," *Molecular Medicine Reports*, vol. 17, no. 3, 2018.
- [236] Y. Chu, M. Jiang, F. du et al., "miR-204-5p suppresses hepatocellular cancer proliferation by regulating homeoprotein SIX1 expression," *FEBS Open Bio*, vol. 8, no. 2, pp. 189–200, 2018.
- [237] Y. Ye, J. Zhuang, G. Wang et al., "MicroRNA-495 suppresses cell proliferation and invasion of hepatocellular carcinoma by directly targeting insulin-like growth factor receptor-1," *Experimental and Therapeutic Medicine*, vol. 15, no. 1, pp. 1150–1158, 2018.
- [238] D. Jiang, W. C. Cho, Z. Li et al., "MiR-758-3p suppresses proliferation, migration and invasion of hepatocellular carcinoma cells via targeting MDM2 and mTOR," *Biomedicine & Pharmacotherapy*, vol. 17, no. 3, pp. 535–544, 2017.
- [239] S. Zhang, Q. Liu, Q. Zhang, and L. Liu, "MicroRNA-30a-5p suppresses proliferation, invasion and tumor growth of hepatocellular cancer cells via targeting FOXA1," *Oncology Letters*, vol. 14, no. 4, pp. 5018–5026, 2017.
- [240] L. Yang, F. Peng, J. Qin, H. Zhou, and B. Wang, "Downregulation of microRNA-196a inhibits human liver cancer cell proliferation and invasion by targeting FOXO1," *Oncology Reports*, vol. 38, no. 4, pp. 2148–2154, 2017.
- [241] K. Zhou, X. Luo, Y. Wang, D. Cao, and G. Sun, "MicroRNA-30a suppresses tumor progression by blocking Ras/Raf/MEK/ERK signaling pathway in hepatocellular carcinoma," *Biomedicine & Pharmacotherapy*, vol. 93, pp. 1025–1032, 2017.
- [242] S. Hu, Y. Ran, W. Chen, Y. Zhang, and Y. Xu, "MicroRNA-326 inhibits cell proliferation and invasion, activating apoptosis in hepatocellular carcinoma by directly targeting LIM and SH3 protein 1," *Oncology Reports*, vol. 38, no. 3, pp. 1569–1578, 2017.
- [243] Q. Li, S. Li, Y. Wu, and F. Gao, "miRNA-708 functions as a tumour suppressor in hepatocellular carcinoma by targeting SMAD3," *Oncology Letters*, vol. 14, no. 2, pp. 2552–2558, 2017.
- [244] X. Ma, B. Zhuang, and W. Li, "MicroRNA-296-5p downregulated AKT2 to inhibit hepatocellular carcinoma cell proliferation, migration and invasion," *Molecular Medicine Reports*, vol. 16, no. 2, pp. 1565–1572, 2017.
- [245] Y. Liu, H. Huang, M. Liu, Q. Wu, W. Li, and J. Zhang, "MicroRNA-24-1 suppresses mouse hepatoma cell invasion and metastasis via directly targeting O-GlcNAc transferase," *Biomedicine & Pharmacotherapy*, vol. 91, pp. 731–738, 2017.
- [246] F. Cartier, E. Indersie, S. Lesjean et al., "New tumor suppressor microRNAs target glypican-3 in human liver cancer," *Oncotarget*, vol. 8, no. 25, pp. 41211–41226, 2017.
- [247] G. Jiang, L. Wen, W. Deng, Z. Jian, and H. Zheng, "Regulatory role of miR-211-5p in hepatocellular carcinoma metastasis by targeting ZEB2," *Biomedicine & Pharmacotherapy*, vol. 90, pp. 806–812, 2017.
- [248] C. Zuo, X. Sheng, Z. Liu et al., "MicroRNA-138 enhances TRAIL-induced apoptosis through interferon-stimulated gene 15 downregulation in hepatocellular carcinoma cells," *Tumor Biology*, vol. 39, no. 6, 2017.
- [249] W. Wang, H. Zhang, M. Tang et al., "MicroRNA-592 targets IGF-1R to suppress cellular proliferation, migration and invasion in hepatocellular carcinoma," *Oncology Letters*, vol. 13, no. 5, pp. 3522–3528, 2017.
- [250] M. Li, Y. Yang, Y. Kuang et al., "miR-365 induces hepatocellular carcinoma cell apoptosis through targeting Bcl-2," *Experimental and Therapeutic Medicine*, vol. 13, no. 5, pp. 2279–2285, 2017.
- [251] M. Zhang, M. Li, N. Li et al., "miR-217 suppresses proliferation, migration, and invasion promoting apoptosis via targeting MTDH in hepatocellular carcinoma," *Oncology Reports*, vol. 37, no. 3, pp. 1772–1778, 2017.
- [252] L. Zhou, S. Liu, M. Han et al., "MicroRNA-185 induces potent autophagy via AKT signaling in hepatocellular carcinoma," *Tumor Biology*, vol. 39, no. 2, 2017.
- [253] H. Ge, D. Zou, Y. Wang, H. Jiang, and L. Wang, "MicroRNA-377 downregulates Bcl-xL and increases apoptosis in hepatocellular carcinoma cells," *Oncology Research Featuring Pre-clinical and Clinical Cancer Therapeutics*, vol. 25, no. 1, pp. 29–34, 2017.
- [254] L.-J. Luo, L.-P. Zhang, C.-Y. Duan et al., "The inhibition role of miR-22 in hepatocellular carcinoma cell migration and invasion via targeting CD147," *Cancer Cell International*, vol. 17, no. 1, 2017.
- [255] X. Wei, C. Tang, X. Lu et al., "MiR-101 targets DUSP1 to regulate the TGF- β secretion in sorafenib inhibits macrophage-induced growth of hepatocarcinoma," *Oncotarget*, vol. 6, no. 21, pp. 18389–18405, 2015.
- [256] F. Zheng, Y.-J. Liao, M.-Y. Cai et al., "Systemic delivery of microRNA-101 potently inhibits hepatocellular carcinoma in vivo by repressing multiple targets," *PLoS Genetics*, vol. 11, no. 2, article e1004873, 2015.
- [257] L. Xu, S. Beckebaum, S. Iacob et al., "MicroRNA-101 inhibits human hepatocellular carcinoma progression through EZH2 downregulation and increased cytostatic drug sensitivity," *Journal of Hepatology*, vol. 60, no. 3, pp. 590–598, 2014.
- [258] W. Li, S. Shen, S. Wu, Z. Chen, C. Hu, and R. Yan, "Regulation of tumorigenesis and metastasis of hepatocellular carcinoma tumor endothelial cells by microRNA-3178 and underlying mechanism," *Biochemical and biophysical research communications*, vol. 464, no. 3, pp. 881–887, 2015.

- [259] H. Okada, M. Honda, J. S. Campbell et al., "Inhibition of microRNA-214 ameliorates hepatic fibrosis and tumor incidence in platelet-derived growth factor C transgenic mice," *Cancer Science*, vol. 106, no. 9, pp. 1143–1152, 2015.
- [260] X. Wang, Y. Ren, X. Yang et al., "miR-190a inhibits epithelial-mesenchymal transition of hepatoma cells via targeting the long non-coding RNA *lincRNA*," *FEBS Letters*, vol. 589, no. 24PartB, pp. 4079–4087, 2015.
- [261] X. Yang, J. Ye, H. Yan et al., "MiR-491 attenuates cancer stem cells-like properties of hepatocellular carcinoma by inhibition of GIT-1/NF- κ B-mediated EMT," *Tumor Biology*, vol. 37, no. 1, pp. 201–209, 2016.
- [262] W. Z. Ding, Q. F. Ni, Y. T. Lu et al., "MicroRNA-497 regulates cell proliferation in hepatocellular carcinoma," *Oncology Letters*, vol. 11, no. 2, pp. 1081–1088, 2016.
- [263] Y. Huang, J. Liu, L. Fan et al., "miR-663 overexpression induced by endoplasmic reticulum stress modulates hepatocellular carcinoma cell apoptosis via transforming growth factor β 1," *Oncotargets and Therapy*, vol. 9, pp. 1623–1633, 2016.
- [264] G. S. Chen, N. Zhou, J.-Q. Li, T. Li, Z.-Q. Zhang, and Z.-Z. Si, "Restoration of miR-20a expression suppresses cell proliferation, migration, and invasion in HepG2 cells," *Oncotargets and Therapy*, vol. 9, pp. 3067–3076, 2016.
- [265] Q. ZHANG, S. ZHAO, X. PANG, and B. CHI, "MicroRNA-381 suppresses cell growth and invasion by targeting the liver receptor homolog-1 in hepatocellular carcinoma," *Oncology Reports*, vol. 35, no. 3, pp. 1831–1840, 2016.
- [266] N. Zhao, H. Sun, B. Sun et al., "miR-27a-3p suppresses tumor metastasis and VM by down-regulating VE-cadherin expression and inhibiting EMT: an essential role for Twist-1 in HCC," *Scientific Reports*, vol. 6, no. 1, article 23091, 2016.
- [267] Y. Wang, B. Sun, X. Zhao et al., "Twist1-related miR-26b-5p suppresses epithelial-mesenchymal transition, migration and invasion by targeting SMAD1 in hepatocellular carcinoma," *Oncotarget*, vol. 7, no. 17, pp. 24383–24401, 2016.
- [268] W. Li, H. Dai, Q. Ou, G. Zuo, and C. Liu, "Overexpression of microRNA-30a-5p inhibits liver cancer cell proliferation and induces apoptosis by targeting MTDH/PTEN/AKT pathway," *Tumor Biology*, vol. 37, no. 5, pp. 5885–5895, 2016.
- [269] S.-Y. Han, H.-B. Han, X.-Y. Tian et al., "MicroRNA-33a-3p suppresses cell migration and invasion by directly targeting PBX3 in human hepatocellular carcinoma," *Oncotarget*, vol. 7, no. 27, pp. 42461–42473, 2016.
- [270] D. Zhou, X. Wang, Y. Wang et al., "MicroRNA-145 inhibits hepatic stellate cell activation and proliferation by targeting ZEB2 through Wnt/ β -catenin pathway," *Molecular Immunology*, vol. 75, pp. 151–160, 2016.
- [271] M. Hu, M. Wang, H. Lu et al., "Loss of miR-1258 contributes to carcinogenesis and progression of liver cancer through targeting CDC28 protein kinase regulatory subunit 1B," *Oncotarget*, vol. 7, no. 28, pp. 43419–43431, 2016.
- [272] H. Zhu, G. Wang, X. Zhou et al., "miR-1299 suppresses cell proliferation of hepatocellular carcinoma (HCC) by targeting CDK6," *Biomedicine & Pharmacotherapy*, vol. 83, pp. 792–797, 2016.
- [273] X. Cui, Z. Li, J. Gao, P.-J. Gao, Y.-B. Ni, and J.-Y. Zhu, "Elevated CXCL1 increases hepatocellular carcinoma aggressiveness and is inhibited by miRNA-200a," *Oncotarget*, vol. 7, no. 40, pp. 65052–65066, 2016.
- [274] R. A. Youness, H. M. El-Tayebi, R. A. Assal, K. Hosny, G. Esmat, and A. I. Abdelaziz, "MicroRNA-486-5p enhances hepatocellular carcinoma tumor suppression through repression of IGF-1R and its downstream mTOR, STAT3 and c-Myc," *Oncology Letters*, vol. 12, no. 4, pp. 2567–2573, 2016.
- [275] J. M. Lee, M. J. Heo, C. G. Lee, Y. M. Yang, and S. G. Kim, "Increase of miR-199a-5p by protoporphyrin IX, a photocatalyzer, directly inhibits E2F3, sensitizing mesenchymal tumor cells to anti-cancer agents," *Oncotarget*, vol. 6, no. 6, pp. 3918–3931, 2015.
- [276] J. Liu, J. Yan, C. Zhou, Q. Ma, Q. Jin, and Z. Yang, "miR-1285-3p acts as a potential tumor suppressor miRNA via downregulating JUN expression in hepatocellular carcinoma," *Tumor Biology*, vol. 36, no. 1, pp. 219–225, 2015.
- [277] S. Chen, B. Liu, J. Xu et al., "MiR-449a suppresses the epithelial-mesenchymal transition and metastasis of hepatocellular carcinoma by multiple targets," *BMC Cancer*, vol. 15, no. 1, p. 706, 2015.
- [278] D. Cai, K. He, S. Chang, D. Tong, and C. Huang, "MicroRNA-302b enhances the sensitivity of hepatocellular carcinoma cell lines to 5-FU via targeting Mcl-1 and DPYD," *International Journal of Molecular Sciences*, vol. 16, no. 10, pp. 23668–23682, 2015.
- [279] L. Cao, B. Xie, X. Yang et al., "MiR-324-5p suppresses hepatocellular carcinoma cell invasion by counteracting ECM degradation through post-transcriptionally downregulating ETS1 and SP1," *PLoS One*, vol. 10, no. 7, article e0133074, 2015.
- [280] H. Li, Q. Sun, B. Han, X. Yu, B. Hu, and S. Hu, "MiR-26b inhibits hepatocellular carcinoma cell proliferation, migration, and invasion by targeting EphA2," *International Journal of Clinical and Experimental Pathology*, vol. 8, no. 5, pp. 4782–4790, 2015.
- [281] H. Zhang, Z. Feng, R. Huang, Z. Xia, G. Xiang, and J. Zhang, "MicroRNA-449 suppresses proliferation of hepatoma cell lines through blockade lipid metabolic pathway related to SIRT1," *International Journal of Oncology*, vol. 45, no. 5, pp. 2143–2152, 2014.
- [282] X. X. He, A. Y. Guo, C. R. Xu et al., "Bioinformatics analysis identifies miR-221 as a core regulator in hepatocellular carcinoma and its silencing suppresses tumor properties," *Oncology Reports*, vol. 32, no. 3, pp. 1200–1210, 2014.
- [283] W. Liu, C. Xu, H. Wan et al., "MicroRNA-206 overexpression promotes apoptosis, induces cell cycle arrest and inhibits the migration of human hepatocellular carcinoma HepG2 cells," *International Journal of Molecular Medicine*, vol. 34, no. 2, pp. 420–428, 2014.
- [284] L. Yunqiao, H. Vanke, X. Jun, and G. Tangmeng, "MicroRNA-206, down-regulated in hepatocellular carcinoma, suppresses cell proliferation and promotes apoptosis," *Hepato-Gastroenterology*, vol. 61, no. 133, pp. 1302–1307, 2014.
- [285] Y.-W. Dang, J. Zeng, R.-Q. He, M.-H. Rong, D.-Z. Luo, and G. Chen, "Effects of miR-152 on cell growth inhibition, motility suppression and apoptosis induction in hepatocellular carcinoma cells," *Asian Pacific Journal of Cancer Prevention*, vol. 15, no. 12, pp. 4969–4976, 2014.
- [286] J. Zhang, H. Jin, H. Liu et al., "MiRNA-99a directly regulates AGO2 through translational repression in hepatocellular carcinoma," *Oncogene*, vol. 3, no. 4, article e97, 2014.
- [287] W. Dai, C. Wang, F. Wang et al., "Anti-miR-197 inhibits migration in HCC cells by targeting KAI 1/CD82," *Biochemical and Biophysical Research Communications*, vol. 446, no. 2, pp. 541–548, 2014.

- [288] N. Zhao, R. Wang, L. Zhou, Y. Zhu, J. Gong, and S.-M. Zhuang, "MicroRNA-26b suppresses the NF- κ B signaling and enhances the chemosensitivity of hepatocellular carcinoma cells by targeting TAK1 and TAB3," *Molecular Cancer*, vol. 13, no. 1, p. 35, 2014.
- [289] Y. M. Liu, Y. Xia, W. Dai et al., "Cholesterol-conjugated let-7amimics: antitumor efficacy on hepatocellular carcinoma in vitro and in a preclinical orthotopic xenograft model of systemic therapy," *BMC Cancer*, vol. 14, no. 1, p. 889, 2014.
- [290] K. Zhu, Q. Pan, L. Q. Jia et al., "MiR-302c inhibits tumor growth of hepatocellular carcinoma by suppressing the endothelial-mesenchymal transition of endothelial cells," *Scientific Reports*, vol. 4, 2014.
- [291] Q. Liu, Y. Xu, S. Wei et al., "miRNA-148b suppresses hepatic cancer stem cell by targeting neuropilin-1," *Bioscience Reports*, vol. 35, no. 4, 2015.
- [292] W. Cui, Z. Huang, H. He et al., "MiR-1188 at the imprinted Dlk1-Dio3 domain acts as a tumor suppressor in hepatoma cells," *Molecular Biology of the Cell*, vol. 26, no. 8, pp. 1416–1427, 2015.
- [293] D. Ma, X. Gao, Z. Liu, X. Lu, H. Ju, and N. Zhang, "Exosome-transferred long non-coding RNA ASMTL-AS1 contributes to malignant phenotypes in residual hepatocellular carcinoma after insufficient radiofrequency ablation," *Cell Proliferation*, vol. 53, no. 9, 2020.
- [294] T. Guo, C. Gong, P. Wu et al., "LINC00662 promotes hepatocellular carcinoma progression via altering genomic methylation profiles," *Cell Death and Differentiation*, vol. 27, no. 7, pp. 2191–2205, 2020.