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.

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 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 DNMT12); 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 implicated 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.  |
|---------------|--------------------------|-------|
| ACSL4         | Hypomethylation          |       |
| ALDH3A1       | Hypomethylation          | [217] |
| APOA5         | Hypermethylation         |       |
| CLDN15        | Hypomethylation          |       |
| CDKN2A        | Hypermethylation         | [6]   |
| CYP7A1        | Hypomethylation          | [217] |
| DEFB119       | Hypomethylation          | [6]   |
| DPP6          | Hypomethylation          |       |
| ENDOD1        | Hypermethylation         |       |
| EZR           | Hypermethylation         | [217] |
| GLUL          | Hypomethylation          |       |
| GZMB          | Hypomethylation          | [6]   |
| MIR21         | Hypermethylation         | [218] |
| Mxy1g         | Hypermethylation         | [219] |
| NEFH          | Hypermethylation         | [13]  |
| NKX3-2-2      | Hypermethylation         |       |
| NDRG2         | Hypermethylation         | [6]   |
| PDE1A         | Hypomethylation          |       |
| PHYHD1        | Hypermethylation         | [217] |
| PRH2          | Hypermethylation         | [6]   |
| RASSF1A       | Hypermethylation         | [220] |
| RP11-59D14.1  | Hypermethylation         | [15]  |
| SCAND3        | Hypermethylation         | [219] |
| SPP1          | Hypomethylation          | [217] |
| SPRR2A        | Hypomethylation          | [6]   |
| SLC25A47      | Hypermethylation         | [6]   |
| SLC25A47      | Hypermethylation         | [217] |
| SLC39A12      | Hypermethylation         | [6]   |
| SMPD3         | Hypermethylation         | [13]  |
| SFN           | Hypomethylation          | [217] |
| SGCA          | Hypomethylation          |       |
| TXB4          | Hypermethylation         | [6]   |
| TCAM1P-004    | Hypermethylation         | [15]  |
| TKT           | Hypermethylation         | [217] |
| VTRNA2-1      | Hypermethylation         | [221] |
| ZBPB          | 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; DEF8119: Defensin β 119; DPP6: Dipetidyl peptidase 6; ENDOD1: Endonuclease Domain Containing 1; EZR: Ezrin; GLUL: Glutamate-Ammonia Ligase; GZMB: Granzyme B; MIR21: microRNA-21; Mxy1g: 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 Oxidase Domain Containing 1; PRH2: Ras association domain family 1 isoform A; SCAND3: SCAN domain containing 3; SFN: Stat3fins; SGCA: a-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; TXB4: T-box 4; TKT: Transketolase; VTRNA2-1: Vault RNA 2-1; ZBPB: Zona pellucida binding protein.

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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 the former to S-adenosyl-L-methionine, the donor of...
DNMT1

a derivative of 5-AZA, was reported to downregulate ALB upstream of the liver-specific miR-122, and the resulting effects on the tumor.

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

ALB: albumin; 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; HIF-1α: hypoxia-inducible factor 1α; 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.

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 demethylation 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 annullled 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 DNMT3b 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 μM, it encouraged cellular growth, while at higher concentration within the range of 10–40 μM, 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 winding 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
As is shown, the most common site for such modifications occurs on specific enzyme in glycolysis [66], and HDAC2 found to suppress fructose-1,6-bisphosphatase [65]. The upregulation of HDAC1 and HDAC3 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 and 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 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.

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

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

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 NKG2D 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, IncRNA-uco002mbe.2, which was increased post-TSA-treatment [78]. The proposed mechanism delineates an interaction between IncRNA-uco002mbe.2 and heterogeneous nuclear ribonucleoprotein A2B1 (hnRNP A2B1) 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 coconitantly 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, 18F probes have been used as PET tracers to monitor angiogenic progression following PANB therapy, through imaging of integrin αvβ3. 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, several of 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 constituted 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 boost of cytokotoxic effects of cytokine-induced killer cells [97]. Recently, VORN was assessed alongside zebularine as to its effect on Suppressors of cytokine signaling 1 (SOCS-1) and Suppressor of cytokine signaling 3 (SOCS-3) expression [98]. Despite both suppressing cellular growth, only VORN demonstrated an apoptotic effect and correlated with an upregulation of SOCS-1 and SOCS-3.

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].

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, another RNase (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 and a normal miRNomes 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 microprocessor 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 TRP2-bound enzyme Dicer, another RNase III, which clips off the loop, producing a double-stranded miRNA (ds-miRNA or miR/miRNA duplex) (Figure 2). The Argonaut 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
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 relatively 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 metallopeptidase 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-tranfected 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 posttranscriptionally 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 IKKa/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 FOXM1, 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 overly expressed 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 Snaill [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 mouse 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 confirmed a 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 SD1 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 IncRNA nuclear-enriched abundant transcripts 1 and 2 (NEAT1 and NEAT2) [129]. On top of that, miR-101 subverted the TGF-β1-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 modifiers, miR-101 has been tried as a part of several combinatorial regimes. Synergy was reported with liposomal doxorubicin [131] and the IncRNA 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
| MicroRNA | Expression changes associated with therapeutic effects | Effect | Targets (and the direction of their therapeutic regulation) | Reference |
|----------|------------------------------------------------------|--------|------------------------------------------------------------|-----------|
| let-7c   | Upregulation                                         | Induction of apoptosis and inhibition of proliferation | LIN28B, ARID3B, Bcl-xL, and c-Myc (downregulation) | [227]     |
| miR-663b | Upregulation                                         | Suppression of tumor proliferation and invasiveness | GAB2 (downregulation) | [228]     |
| miR26a   | Upregulation                                         | Growth inhibition, migration, invasion, colony formation; initiation of hepatoselective apoptosis. Enhancement of chemosensitivity | CCND2, IL-6, and PIK3C2α (downregulation) | [229, 230] |
| miR-122  | Upregulation                                         | Suppression of proliferation, migration, and invasion; initiation of apoptosis | SETDB1 (downregulation) | [231]     |
| miR-621  | Upregulation                                         | Inhibition of proliferation, EMT, migration, and invasion | SIX1 (downregulation) | [232]     |
| miR-299-5p | Downregulation                                   | Inhibition of proliferation and invasion | FOXO1 (upregulation) | [240]     |
| miR-577  | Upregulation                                         | Induction of apoptosis | KRAS (downregulation) | [241]     |
| miR-501-3p | Upregulation                                    | Induction of apoptosis | LASSP1 (downregulation) | [242]     |
| miR-378a | Upregulation                                         | Induction of apoptosis | ZEB2 (downregulation) | [247]     |
| miR-204-5p | Upregulation                                   | Induction of proliferation and inhibition of c-Myc at the protein level and suppression of its O-GlcNAcylation; reduction of metastatic potential | OGT (downregulation) | [245]     |
| miR-30a-3p | Upregulation                                   | Inhibition of proliferation and invasion | FOXA1 (downregulation) | [239]     |
| miR-196a | Downregulation                                         | Inhibition of proliferation and invasion | FOXO1 (upregulation) | [240]     |
| miR-30a  | Upregulation                                         | Inhibition of proliferation and invasion | FOXA1 (downregulation) | [239]     |
| miR-376b-3p | Upregulation                                | Inhibition of proliferation and apoptosis; enhancement of drug sensitivity | ZEB2 (downregulation) | [247]     |
| miR-548aa | Upregulation                                       | Promotion of TRAIL-induced apoptosis | ISG15 (downregulation) | [248]     |
| miR-548v  | Upregulation                                         | Inhibition of proliferation, migration, and invasion | IGF-1R (downregulation) | [249]     |
| miR-4510  | Upregulation                                         | Initiation of apoptosis | Bcl-2 (downregulation) | [250]     |
| MicroRNA | Expression changes associated with therapeutic effects | Effect | Targets (and the direction of their therapeutic regulation) | Reference |
|----------|--------------------------------------------------------|--------|----------------------------------------------------------|-----------|
| miR-217  | Upregulation                                           | Suppression of proliferation, migration, and invasion; initiation apoptosis | MTDH (downregulation) | [251]     |
| miR-199a-5p | Upregulation                               | Decreased cell viability and colony formation; cell cycle arrest | CLTC (downregulation) | [119]     |
| miR-185  | Upregulation                                           | Inhibition of proliferation; G0/G1 arrest; promotion of apoptosis | RHEB, RICTOR, and AKT1 (downregulation) | [252]     |
| miR-503  | Upregulation                                           | Repression of proliferation and sensitization to anticancer drugs | EIF4E (downregulation) | [124]     |
| miR-377  | Upregulation                                           | Inhibition of invasion and migration; repression of EMT | PRMT1 (downregulation) | [122]     |
| miR-199a-3p | Upregulation                  | Suppression of proliferation and induction of apoptosis | Bcl-xl (downregulation) | [253]     |
| miR-22   | Upregulation                                           | Growth inhibition and induction of apoptosis | ZHX1 and PUMA (upregulation) and Bcl-2 (downregulation) | [166]     |
|          | Downregulation                                         | Repression of TGF-β and CD206 in M2 cells; inhibition of macrophage-driven HCC | DUSP1 (upregulation) | [255]     |
| miR-101  | Upregulation                                           | 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 | TGF-βR1, Smad2, SDF1, VE-cadherin, EZH2, COX2, STMN1, and ROCK2 (downregulation) | [128, 256, 257] |
| miR-3178 | Upregulation                                           | Inhibition of proliferation, G1 arrest, and promotion of apoptosis | EGR3 (downregulation) | [258]     |
| LNA-antimiR-214 | Upregulation                      | Reduction in fibrosis | miR-214 (downregulation) | [259]     |
| miR-190a | Upregulation                                           | Suppression of migration and invasion | treRNA (downregulation) | [260]     |
| miR-491  | Upregulation                                           | Lowering of cancer stem cell-like properties; inhibition of extracellular signal-regulated kinases | GIT-1 (downregulation) | [261]     |
| miR-497  | Upregulation                                           | Inhibition of colony formation and tumor growth | IGF-1R (downregulation) | [262]     |
| miR-663  | Downregulation                                         | Inhibition of proliferation and promotion of apoptosis | TGFβ1 (upregulation) | [263]     |
| miR-20a  | Upregulation                                           | Promotion of apoptosis; inhibition of proliferation, invasion, and migration | CCND1 (downregulation) | [264]     |
| miR-148a | Upregulation                                           | Suppression of tumor growth and malignancy. Promotion of differentiated phenotype | IKKα (downregulation) | [110]     |
| miR-381  | Upregulation                                           | Inhibition of proliferation, colony formation, invasion, and induction of G0/G1 arrest | LRH-1 (downregulation) | [265]     |
| miR-27a-3p | Upregulation                           | Inhibition of EMT, metastasis, and VM | VE-cadherin (downregulation) | [266]     |
| miR-26b-5p | Upregulation                          | Suppression of Twist1-induced EMT | SMAD1 (downregulation) | [267]     |
| miR-30a-5p | Upregulation                           | Inhibition of proliferation, colony formation, and induction of apoptosis | MTDH (downregulation) | [268]     |
| miR-33a-3p | Upregulation                           | Suppression of cellular growth and migration/invasion | PBX3 (downregulation) | [269]     |
| miR-145  | Upregulation                                           | Inhibition of activation and proliferation of hepatic stellate cells | ZEB2 (downregulation) | [270]     |
| miR-1258 | Upregulation                                           | Inhibition of proliferation, G0/G1 arrest, and induction of apoptosis | CKS1B (downregulation) | [271]     |
| MicroRNA  | Expression changes associated with therapeutic effects | Effect                                                                 | Targets (and the direction of their therapeutic regulation) | Reference |
|----------|------------------------------------------------------|-----------------------------------------------------------------------|-----------------------------------------------------------|------------|
| miR-1299 | Upregulation                                         | G0/G1 arrest and inhibition of proliferation                          | CDK6 (downregulation)                                    | [272]      |
| miR-200a | Upregulation                                         | Inhibition of EMT and decreased mitochondrial metabolism               | CXCL1 (downregulation)                                   | [273]      |
| miR-486-5p | Upregulation                               | Repression of proliferation, cellular viability, migration, and clonogenicity | IGF-1R, mTOR, STAT3, and c-Myc (downregulation)           | [274]      |
| miR-199a-5p | Upregulation                                | Inhibition of proliferation, migration/invasion, and synergized with chemotherapeutics | E2F3 (downregulation)                                   | [275]      |
| miR-1285-3p | Upregulation                                | Inhibition of proliferation                                          | JUN (downregulation)                                    | [276]      |
| miR-449a | Upregulation                                         | Inhibition of motility and pulmonary metastasis; increase of epithelial markers and reduction of mesenchymal markers; reduction of Snail nuclear accumulation | FOS and Met (downregulation)                           | [277]      |
| miR-302b | Upregulation                                         | sensitization to 5-FU                                                | MCL-1 and DPYD (downregulation)                          | [278]      |
| miR-143  | Downregulation                                       | Inhibition of proliferation due to a G0/G1 arrest; induction of apoptosis | TLR2, NF-κB, MMP-2, MMP-9, CD44, MMP14, integrin β1, and integrin β4 (downregulation) | [279]      |
| miR-324-5p | Upregulation                                | Subduing invasiveness and metastatic capacity; downregulation of MMP2 and MMP9 | ETS1 and SP1 (downregulation)                           | [279]      |
| miR-26b  | Upregulation                                         | Inhibition of proliferation, invasion, and migration                  | EphA2 (downregulation)                                  | [280]      |
| miR-449  | Upregulation                                        | Suppression of DNA replication, mitotic entry, and cellular proliferation | SIRT1 and SREBP-1c (downregulation)                     | [281]      |
| miR-221  | Downregulation                                       | Lowering of proliferation and clonogenicity; inhibition of migration/invasion; induction of G1 arrest and apoptosis | BMF, BBC3, and ANGPTL2 (downregulation)                 | [282]      |
| miR-206  | Upregulation                                         | Cell cycle arrest and inhibition of proliferation, invasion, and migration. Induction of apoptosis | Notch3, HES1, Bcl-2, and MMP-9 (downregulation) and p57, Bax, and cleaved caspase 3 (upregulation) | [283, 284] |
| miR-148a | Upregulation                                         | Repression of EMT and pulmonary metastasis; increase of epithelial markers; reduction of mesenchymal markers | Met (downregulation)                                    | [111]      |
| miR-152  | Upregulation                                         | Inhibition of proliferation, cellular motility, and promotion of apoptosis | TNFRF6B (downregulation)                                | [285]      |
| miR-99a  | Upregulation                                         | Inhibition of proliferation                                          | Ago2 (downregulation)                                   | [286]      |
| Anti-miR-197 | Upregulation                                | Inhibition of migration and invasion; upregulation of CD82             | miR-197 (downregulation)                                | [287]      |
| miR-26b  | Upregulation                                         | Sensitization of cells to doxorubicin-induced apoptosis               | TAK1 and TAB3 (downregulation)                           | [288]      |
| let-7a   | Upregulation                                         | Inhibition of local invasion and migration                             | KRAS, HRAS, and NRAS (downregulation)                   | [289]      |
| miR-126-3p | Upregulation                               | Inhibition of migration and invasion; suppression of capillary tube formation; reduction of tumor volume and microvessel density | LRP6 and PIK3R2 (downregulation)                       | [104]      |
| miR-302c | Upregulation                                         | Attenuation of HUVECs motility; upregulation of VE-cadherin; downregulation of β-catenin, FSP1, and α-SMA; growth inhibition in cocultures | MTDH (downregulation)                                  | [290]      |
### Table 4: Continued.

| MicroRNA | Expression changes associated with therapeutic effects | Effect | Targets (and the direction of their therapeutic regulation) | Reference |
|----------|-----------------------------------------------------|--------|----------------------------------------------------------|-----------|
| miR-148b | Upregulation                                        | Inhibition of proliferation, metastasis and angiogenesis. Improvement of chemosensitivity | NRPI1 (downregulation) | [291] |
| miR-1188 | Upregulation                                        | Inhibition of proliferation, migration, invasion, and promotion of apoptosis | Bcl-2 and Sp1 (downregulation) | [292] |
| miR-126  | Upregulation                                        | Inhibition of proliferation, cell cycle arrest, and induction of apoptosis | SOX2 (downregulation) | [105] |

ADAM10: ADAM metallopeptidase domain 10; ADAM17: ADAM metallopeptidase domain 17; Ago2: Argonaute 2; AKT1: AKT serine/threonine kinase 1; AKT2: AKT serine/threonine kinase 2; ANGPTL2: Angiopoietin-like 2; ARID3B: AT-rich interaction domain 3B; Bcl: B-cell lymphoma 2 apoptosis regulator; Bcl-w: Bcl-2-like protein 2; Bcl-xL: Bcl-2-like protein 2; CDKN1A: CDK6: cyclin-dependent kinase 2; CDKN2A: CCND1: Cyclin D1; CDKN2B: CCND2: Cyclin D2; CDKN2C: CCNG1: CD133: Cyclin G1; CDK6: cyclin-dependent kinase 6; c-Raf: Raf-1 protooncogene, serine/threonine kinase; CXCL1: C-X-C motif chemokine ligand 1; DUSP1: Dual specificity phosphatase 1; EP300: ETS protooncogene 1; EZH2: enhancer of zeste 2 polycomb repressive complex 2 subunit; FOXO1: Forkhead box factor 1; GAB2: GRB2-associated-binding protein 2; GIT-1: GIT ArfGAP 1; GRB2: GRB2-associated-binding protein 2; HES1: Hairy and enhancer of split-1; HOXA1: Hairy and enhancer of split-1; HOX1: Hox family; IGF1R: insulin-like growth factor 1 receptor; IKK: Inhibitor of kB kinase a; IL-6: interleukin-6; ISG15: interferon-stimulated gene 15; JUN: Jun protooncogene; LRP6: low-density lipoprotein receptor-related protein 6; MCL-1: MCL1 apoptosis regulator; MDM2: MDM2 protooncogene; MET: MEF protooncogene, receptor tyrosine kinase; MMP-2: matrix metalloproteinase-2; MMP-9: matrix metalloproteinase-9; NRP1: Neuropilin-1; OGT: O-GlcNAc transferase; OTUD7B: OTU deubiquitinase 7B; PAx: Pre-B-cell leukemia homeobox 3; PIGF: Platelet-derived growth factor receptor beta; PI3K: Phosphatidylinositol-4-kinase 3; PI3K: Proprotein convertase subtilisin/kexin type 2; PIK3CG: Phosphoinositide-3-kinase catalytic subunit type 2 alpha; PIK3R2: Phosphoinositide-3-kinase regulatory subunit 2; PTM: Protein arginine methyltransferase 1; PTOR: RPTOR-independent companion of MTOR, complex 2; ROCK2: Rho-associated coiled-coil containing protein kinase 2; SDF1: Stromal cell-derived factor 1; SETDB1: SET domain bifurcated histone lysine methyltransferase 1; SIAH1: Siah E3 ubiquitin protein ligase 1; SIRT1: Sirtuin 1; SIX1: SIX homeobox 1; SMAD1: SMAD family member 1; SMAD2: SMAD family member 2; SMAD3: SMAD family member 3; SOX2: sex-determining region Y-box 2; SP1: Sp1 transcription factor; SREBP-1c: Sterol regulatory element binding protein-1c; STAT3: signal transducer and activator of transcription 3; TGF-β: Transforming growth factor beta; TGF-βRI: Transforming growth factor beta receptor 1; TNFRSF6B: Tumor necrosis factor receptor super family 6B; TNIIF2: TNIIF2 interacting protein 2; VEGFR: Vascular endothelial growth factor receptor; ZEB2: Zinc finger E-box binding homeobox 2; ZHX1: Zinc fingers and homeobox 1.
(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 explicated 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 mentioned 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, countering 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-κB 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 antagonist 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 UC001kf0. 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 UC001kf0 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 UC001kf0 correlated with tumoral macrovascular invasion (MVI) and TNM staging of HCC, with higher levels predisposing to poorer prognoses [179]. UC001kf0 boosted tumor proliferation and EMT, presumably through targeting alpha-smooth muscle actin (α-SMA). The authors indicate the potential of UC001kf0 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 knockdown 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.     |
|--------------|-------------------|----------------------------------------------------------------------------------------|----------|
| H1           | Upregulated       | Promoting tumor growth and metastasis; upregulation of IGF2, H3K4me3, and H3K27me3 at the P3 and P4 promoters | [208]    |
| AC006262.5   | Upregulated       | Inhibition of miR-7855-5p and upregulation of BPY2C                                    | [200]    |
| AC092171.4   | Upregulated       | Inhibition of mir-1271 and upregulation of GRB2                                        | [182]    |
| ANCR         | Upregulated       | Enhanced proliferation and EMT; upregulation of HNRNP1 through mir-140-3p sponging    | [151]    |
| ANRIL        | Upregulated       | Inhibition of mir-384 and upregulation of STAT3                                      | [214]    |
| ASMTL-AS1    | Upregulated       | Upregulation of NLK and activation of YAP signaling via mir-342-3p sponging           | [293]    |
| CASC2c       | Downregulated     | Activation of ERK1/2 and Wnt/β-catenin signaling                                      | [201]    |
| CASC15       | Upregulated       | Activation of Wnt/β-catenin signaling via upregulation of SOX4                       | [196]    |
| CRNDE        | Upregulated       | Inhibition of the Hippo pathway                                                       | [210]    |
| CTP1-AS2     | Upregulated       | Sponging of mir-195-5p and enhancing CEP55 expression                                 | [198]    |
| DANC2R       | Upregulated       | Enhanced cell proliferation, colony formation, and autophagy; upregulation of ATG7 and suppression of mir-222-3p | [188]    |
| DDX11-AS1    | Upregulated       | Inhibition of LATS2 expression via EZH2 and DNMT1                                     | [203, 204, 207] |
| DUXAP8       | Upregulated       | Enhanced cell proliferation and EMT; mir-422a sponging and upregulation of PDK2       | [147]    |
| FENDRR       | Downregulated     | Downregulation of GPC3                                                                | [168]    |
| FOXD2-AS1    | Upregulated       | miR-206 sponging and enhanced MAP3K1 signaling                                        | [174]    |
| FOXD3-AS1    | Upregulated       | miR-335 sponging and upregulation of RICTOR                                           | [159]    |
| GAS8-AS1     | Downregulated     | Attenuated GAS8 transcription RNA polymerase II activity                              | [157]    |
| H19          | Upregulated       | Amelioration of resistance to sorafenib and upregulation of mir-675                  | [177]    |
| HAND2-AS1    | Downregulated     | Enhanced proliferation; upregulation of mir-300 and inhibition of SOCS3              | [155]    |
| HBVPTPAP     | Upregulated       | Activation of JAK/STAT signaling                                                     | [186]    |
| HCG18        | Upregulated       | Upregulation of CENPM via sponging of mir-214-3p                                      | [180]    |
| HEIH         | Downregulated     | Suppression of cell proliferation and metastasis; upregulation of mir-199a-3p        | [169]    |
| HLNC1        | Upregulated       | Destabilization of USP49                                                             | [183]    |
| HOTAIR       | Upregulated       | Downregulation of c-Met and miR-34a                                                  | [178, 184] |
| HOXA11-AS    | Upregulated       | Downregulation of miR-506-3p and Slug                                                | [191]    |
| KCNQ1OT1     | Upregulated       | Upregulation of ACER3 via sponging of miR-146a-5p; enhanced sorafenib resistance and PD-L1-mediated immune escape via miR-506 sponging | [197, 205] |
| LALR1        | Upregulated       | Anaplasia and distant metastases; upregulation of SNORD72                            | [154]    |
| LEF1-AS1     | Upregulated       | Enhancement of tumor growth and chemoresistance; inhibition of miR-10a-5p and upregulation of MSI, CDCA7, and EZH2 | [162, 194] |
| LINC00160    | Upregulated       | Inhibition of miR-132 and elevated levels of PIK3R                                  | [144]    |
| LINC00174    | Upregulated       | Enhanced proliferation and metastasis and decreased apoptosis; sponging of miR-320 and upregulation of S100A10 | [152]    |
| LINC00467    | Downregulated     | Sponging of miR-9-5a and consequent upregulation of PPARA                            | [140]    |
| LINC00662    | Upregulated       | Posttranscriptional inhibition of NR4A3                                              | [153]    |
| IncRNA            | Expression in HCC | Effect of dysregulation                                                                                                                                                                                                                                                                                                                                 | Ref.   |
|-------------------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|
| LINC00668         | Upregulated       | Promoting cell proliferation and EMT; sponging of miR-532-5p and consequent upregulation of YY1                                                                                                                                                                                                                                                   | [161]  |
| LINC00978         | Upregulated       | Inhibition of p21 and E-cadherin via EZH2-mediated silencing                                                                                                                                                                                                                                                                                          | [211]  |
| LINC01224         | Upregulated       | Inhibition of miR-330-5p and consequent upregulation of CHEK1                                                                                                                                                                                                                                                                                        | [212]  |
| LINC01278         | Upregulated       | Promoting metastasis; inhibition of miR-1258                                                                                                                                                                                                                                                                                                       | [164]  |
| LINC01296         | Upregulated       | Positive regulation of the miR-26a/PTEN axis                                                                                                                                                                                                                                                                                                       | [137]  |
| LINC01419         | Upregulated       | Histone methylation of the RECK promoter via EZH2                                                                                                                                                                                                                                                                                                     | [173]  |
| Linc-GALH         | Downregulated     | Upregulation of Gankyrin                                                                                                                                                                                                                                                                                                                              | [190]  |
| IncARSR           | Upregulated       | Reduction of YAP1 phosphorylation and activation of IRS2/AKT signaling                                                                                                                                                                                                                                                                                | [156]  |
| IncRNA-POIR       | Upregulated       | Enhanced EMT and sorafenib resistance; sponging of miR-182-5p                                                                                                                                                                                                                                                                                       | [202]  |
| MALAT1             | Upregulated       | Tumor progression and doxorubicin resistance; miR-3129-5p sponging, upregulation of β-catenin                                                                                                                                                                                                                                                        | [199, 209] |
| MFI2-AS1           | Upregulated       | Improved proliferation and metastasis; sponging of miR-134 and upregulation of FOXM1                                                                                                                                                                                                         | [142]  |
| MINCR              | Upregulated       | Enhanced proliferation and inhibition of apoptosis; downregulation of miRNA-107                                                                                                                                                                                                             | [150]  |
| miR503HG           | Downregulated     | Enhanced invasion and metastasis; activation of NF-κB signaling                                                                                                                                                                                                                   | [141]  |
| MSC-AS1            | Upregulated       | Promoting cell proliferation and colony formation; suppression of PGK1                                                                                                                                                                                                                     | [172]  |
| MT1JF              | Downregulated     | Repression of tumor growth; decreased AKT expression                                                                                                                                                                                                                                       | [170]  |
| NEAT1              | Upregulated       | Upregulation of WEE1 through miR-101-3p sponging; inhibition of miR-129-5p                                                                                                                                                                                                               | [129, 138] |
| OIP5-AS1           | Upregulated       | Promoting cell proliferation, migration and angiogenesis. Inhibition of apoptosis; inhibition of the miR-26a-3p and miR-3163                                                                                                                                                                      | [163, 171] |
| OTUD6B-AS1         | Upregulated       | Enhanced proliferation and colony formation; sponging of miR-664b-3p                                                                                                                                                                                                                      | [181]  |
| PICSAR             | Upregulated       | Enhanced proliferation and colony formation; sponging of miR-588                                                                                                                                                                                                                         | [189]  |
| RHPN1-AS1          | Upregulated       | Promoting proliferation, migration and invasion; suppression of miR-485-5p                                                                                                                                                                                                                  | [165]  |
| RUNXI-IT1          | Downregulated     | Desponging of miR-632 and activation of WNT/β-catenin pathway                                                                                                                                                                                                                               | [148]  |
| RUSC1-AS1          | Upregulated       | Enhanced proliferation and reduced apoptosis; miR-7-5p sponging and upregulation of NOTCH3                                                                                                                                                                                                   | [185]  |
| SLC2A1-AS1         | Downregulated     | Suppression of glycolysis in HCC cells; downregulation of GLUT1                                                                                                                                                                                                                           | [158]  |
| SNAI3-AS1          | Upregulated       | Promoting proliferation and metastasis; activation of PEG10 sponging miR-27-3p and miR-34a-5p                                                                                                                                                                                                      | [195]  |
| SNHG1              | Upregulated       | Enhanced tumor progression and metastasis; sponging of miR-377-3p                                                                                                                                                                                                                       | [149]  |
| SNHG5              | Upregulated       | Sponging of miR-26a-5p and upregulation of the downstream target, RNF38                                                                                                                                                                                                                     | [160]  |
| SNHG14             | Upregulated       | Inhibition of miR-656-3p, promotion of migration and invasion                                                                                                                                                                                                                                 | [176, 187] |
| SOX2OT             | Upregulated       | Promoting the Warburg effect and metastasis; upregulation of PKM2 via miR-122-5p inhibition                                                                                                                                                                                                     | [167]  |
| SUMO1P3            | Upregulated       | Enhanced cell proliferation and lymph node metastasis; miR-320a sponging and activation of Wnt/β-catenin signaling                                                                                                                                                                                  | [146]  |
| TCL6               | Downregulated     | Activation of PI3K/AKT signaling via upregulation of miR-106a-5p                                                                                                                                                                                                                           | [145]  |
| TMPO-AS1           | Upregulated       | Promoting proliferation, migration, and invasion; miR-329-3p sponging                                                                                                                                                                                                                     | [166]  |
| TUG1               | Upregulated       | Negative regulation of miR-137 and AKT2 and promoting EMT                                                                                                                                                                                                                                     | [175]  |
| UBE2R2-AS1         | Upregulated       | miR-302b sponging and upregulation of EGFR                                                                                                                                                                                                                                                  | [192]  |
| UC001kfo           | Upregulated       | Enhanced proliferation, macrovascular invasion, and EMT; upregulation of α-SMA                                                                                                                                                                                                             | [179]  |
### Table 5: Continued.

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

ACER3: Alkaline Ceramidase 3; AHCY: Adenosylhomocysteinase; AKT: Protein kinase B; ATG7: Autophagy-related 7; BPY2C: Basic Charge Y-Linked 2C; CDCA7: Cell Division Cycle-Associated 7; CENPM: Centromere Protein M; CEP55: Centrosomal Protein 55; CHEK1: checkpoint kinase 1; c-Met: Tyrosine-protein kinase Met; DNMT1: DNA methyltransferase 1; EGFR: epidermal growth factor receptor; ERK: extracellular signal-regulated kinase; EZH2: enhancer of zeste homolog 2; FOXM1: Forkhead box protein M1; GAS8: growth arrest-specific 8; GLUT1: Glucose transporter 1; GRP3: Glypican 3; GRB2: growth factor receptor-bound protein 2; HNRNPA1: 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; MS1: RNA-binding protein Musashi; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NLK: Nemo-Like Kinase; NOTCH3: Notch Receptor 3; NRA4A3: Nuclear Receptor Subfamily 4 Group A Member 3; p21: cyclin-dependent kinase inhibitor 1; PDK2: Pyruvate dehydrogenase kinase isofrom 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; PTEN: 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; SOCS5: 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/YAP1: Yes-associated protein 1; Y11: 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)/IkB 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 Junonji 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.
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