REVIEW

Modulation of miRNAs by Natural Agents: Nature's way of dealing with cancer

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Accumulating lines of evidence have revealed that microRNAs (miRNAs) play critical roles in many biological processes, such as carcinogenesis, angiogenesis, programmed cell death, cell proliferation, invasion, migration, and differentiation. They act either as tumor suppressors or oncogenes, and alteration in their expression patterns has been linked to onset, progression and chemoresistance of various cancers. Moreover, miRNAs are also crucial for the regulation of cancer stem cells (CSCs) self-renewal and proliferation as well as control of Epithelial-to-Mesenchymal Transition (EMT) of cancer cells. Therefore, exploitation of miRNAs as targets for cancer prevention and therapy could be a promising approach. Several experimental and epidemiologic studies have shown that dietary intake of natural agents such as baicalin, ginsenoside, curcumin, resveratrol, genistein, epigallocatechin-3-gallate (EGCG), indole-3-carbinol, 3,3´-diindolylmethane (DIM) including antioxidants among others is inversely associated with the risk for cancer, demonstrating the inhibitory effects of natural agents on carcinogenesis. Additionally, the anticancer agents from natural agents have been found to inhibit the development and progression of cancer through the regulation of various cancer processes such as apoptosis, cell cycle regulation, differentiation, inflammation, angiogenesis, and metastasis. Importantly, natural agents could significantly impact the expression of tumor-suppressor and oncogenic miRNAs, regulate cellular signaling networks, inhibit cancer cell growth and cancer stem cell self-renewal. This is important for the normalization of altered cellular signaling mechanisms in cancer cells. This postulates a much broader use of natural agents in the prevention and/or treatment of various cancers in combination with conventional chemotherapeutics. However, more *in vitro* mechanistic experiments, *in vivo* animal studies, and clinical trials are warranted to realize the true value of natural agents in the prevention and/or treatment of cancer. Herein, we provide an overview of natural agents' modulation of miRNA expression as well as highlight the significance of these observations as potential new strategies in cancer therapies. This review will help us to understand how miRNAs are regulated by natural agents and also help in the development of effective and secure natural agents for therapeutic purposes.

Keywords: MicroRNA, Natural agents; Phytochemicals; Nutraceuticals; Cancer therapy; Cancer stem cells; Embryonic stem cells; Carcinogenesis

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Introduction

Cancer is a complex, multi-step disease characterized by disruption of the homeostatic balance between cell proliferation and cell death, and uncontrolled, uncoordinated and purposeless clonal expansion leading to tumor formation. Worldwide, it was estimated that 14.1 million new cancer cases and 8.2 million cancer deaths occurred in 2012, with 32.6 million people reported to be living with cancer having been diagnosed in the past five years [1]. It is projected that the number of new cancer cases may increase to 19.3 million by 2025 due to global population aging. Surgery, radiation, and chemotherapy are among the modalities used in cancer treatment, whose goal is to either cure the disease or prolong and improve the patient's quality of life. Although chemotherapy has led to improvement in this aspect, drug resistance and toxicities remains a significant challenge [2]. Thus, there is an urgent need to identify safer but equally effective agents to be used in cancer treatments, which can be found in natural agents.

For many decades, protein-coding genes were the primary focus of cancer research, however, over the past two decades there has been a major paradigm shift with the emerging role of miRNAs and other epigenetic mechanisms as major players [3-5]. Numerous studies have shown that miRNAs not only are involved in the process of cell development and differentiation, but also play a critical role in carcinogenesis [6]. To date, more than 2,400 miRNAs have been identified in humans [7], and it is estimated that more than 30% of human genes may be regulated by miRNAs [8]. Moreover, approximately 50% of the known miRNAs are reported to be located in cancer–associated genomic regions [9] and miRNA dysregulation has been detected in various cancer cells [10]. Therefore, aberrations in miRNA expression patterns are thought to be involved in the progression of human cancers [11].

Emerging data suggest that several classes of naturally occurring, plant-derived compounds (natural agents) could potentially regulate the expression of several miRNAs involved in cancer. 'Natural agents' as referred to here are plant chemicals that have various applications including anti-inflammatory, anti-oxidative, anti-proliferation, anti-bacterial, anti-viral, and anticancer [12]. These agents are widely distributed in various fruits, vegetables, herbs, beverages, and many other dietary supplements. Numerous studies have demonstrated that the intake of fruit- and vegetable-rich foods decreases the occurrence of cancer [13-15]. So far, more than 10,000 natural agents have been identified [16], and a significant number show anticancer potential with no or minimal toxicity to normal cells [17]. Not surprisingly therefore, more than 45% of FDA approved anticancer drugs are derived from plants [18]. Moreover, these natural agents could be used as a single chemotherapeutic agent or in association with standard anticancer drugs. They can increase the efficacy of anticancer drugs synergistically, while reducing the toxic side effects of the standard chemotherapeutic drugs [19, 20]. Generally, they exert their anticancer and other effects through modulation of multiple molecular targets affecting various signaling pathways [16, 21]. This is beneficial as malignant transformation and progression are multistage processes caused by gene alterations in more than one signaling pathway. This is one of the most plausible explanations why monomodal therapy typically fails in cancer treatments as the specific inhibitors often target only a single gene in a signaling pathway [22]. Although natural agents including Traditional Chinese Medicine (TCM) are known to regulate multiple signaling pathways involved in carcinogenesis, the mechanism by which they simultaneously interferes with these pathways remains unclear. One probable explanation is that some botanicals have the capacity to regulate miRNAs associated with cancer [23]. Herein, we provide a brief overview of natural agents' modulation of miRNA expression and their potential role in cancer treatment and prevention.

Brief overview of MicroRNAs (miRNAs)

MicroRNAs (miRNAs) are endogenous, short (18–26 nucleotides long), evolutionarily conserved, non-coding RNAs that regulate gene expression at the post-transcriptional level and play an important role in the regulation of several cellular, physiological, and developmental processes [24]. It is now known that thousands of functional miRNAs exist which are widely expressed in plants and animals and regulate the expression of more than 30% of proteins which are closely related to biological processes, such as cell growth, proliferation, differentiation, migration and apoptosis [25-27].

The biogenesis of miRNAs is well documented (**Figure 1**) and the involvement of miRNAs in regulation of cancer-related events is well established [28]. These small non-coding RNAs are believed to be involved in every single aspect of the development and progression of human cancers. Pertinently, miRNAs are de-regulated in cancer cells with reduced expression of tumor suppressor miRNAs and increased expression of oncogenic miRNAs, relative to normal tissue (**Table 1**). Consequently, miRNAs have been shown to affect cardinal features of cancer such as sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis [29-32] (**Figure 2**). Thus, alteration of miRNA expression and function may contribute to the initiation, maintenance, and progression of tumors as well as to invasiveness, metastasis, and acquisition of drug resistance in cancer [33, 34].

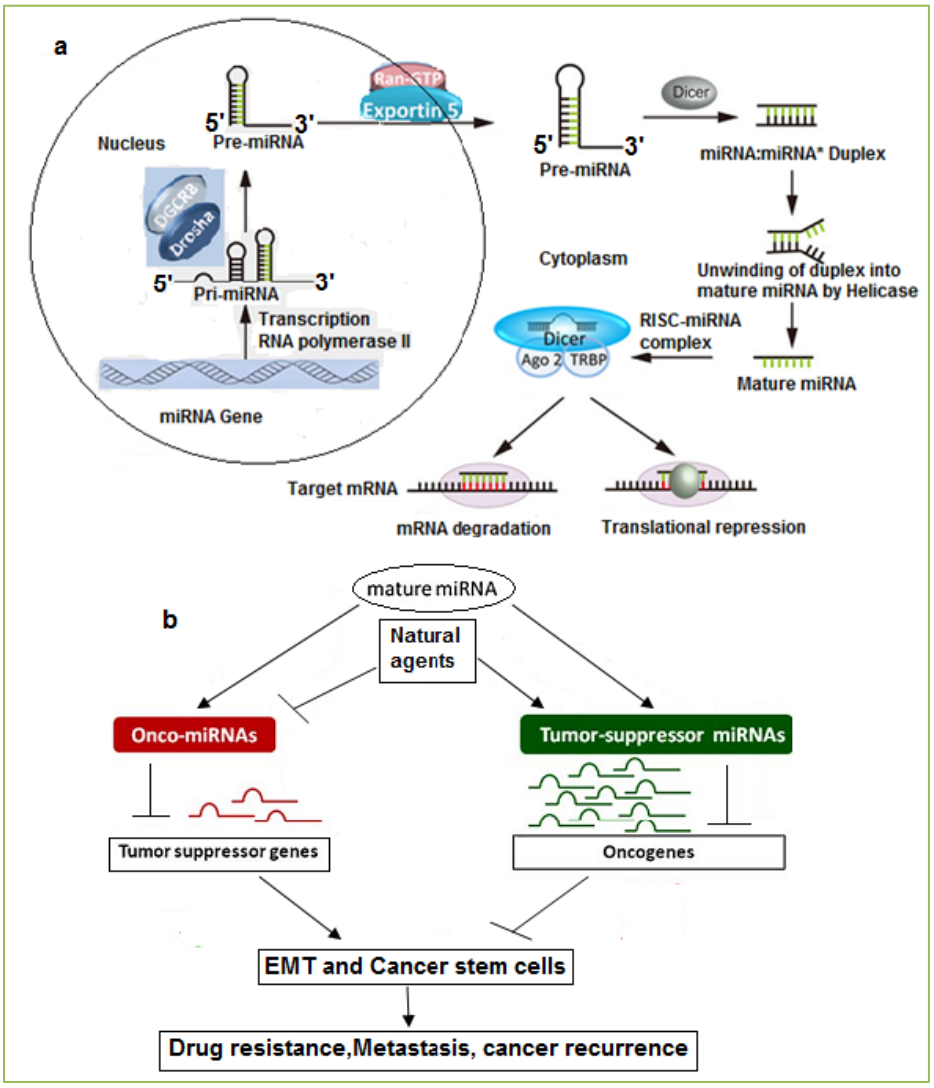

Figure 1. Biogenesis of microRNAs and effect of natural agents on miRNA regulated drug resistance, metastasis and recurrence of cancer. (a) MiRNAs are transcribed by RNA polymerase II into long pri-miRNA, which can be recognized and cleaved in the nucleus by Drosha, resulting in a hairpin precursor form called pre-miRNA. Then, the pre-miRNA is exported from the nucleus to the cytoplasm by Exportin 5 and RanGTP and is further processed by Dicer, to produce a duplex molecule containing single-stranded mature miRNA and a miRNA* fragment. The miRNA: miRNA* duplex is unwound by helicase and the miRNA* fragment is degraded, whereas the mature miRNA molecule binds to an Argonaute (Ago) protein and incorporates into the RNA-induced silencing complex (RISC). The RISC–miRNA complex can then target mRNAs bearing a perfectly complementary target site for degradation or can repress the translation of an mRNA that shows imperfect complementarity with the small RNA. (b) Dependent on various factors, miRNA can have either an oncogenic role if the target mRNA is a tumor suppressor gene, or a tumor suppressive role if the target molecule is an oncogene. Natural agents can impact expression level of miRNAs and participate in gene expression regulation as well as impacting miRNA regulated drug resistance, metastasis and recurrence of cancer. Primary miRNA, pri-miRNA; precursor miRNA, pre-miRNA; Drosha, RNase III endonuclease; DGCR8, Di George syndrome critical region 8; Dicer, RNase III endonuclease; RISC, RNA-induced silencing complex; EMT, epithelial-to-mesenchymal transition.

Since their discovery, miRNAs have provided us with novel insights and ground-breaking impulses to enhance our understanding of molecular biology. In particular, due to their unique role in post-transcriptional regulation, miRNAs are essential to embryonic stem cell (ESC) biology as well as CSC. By serving as buffers to balance between ESC and CSC pluripotency, proliferation, and differentiation, miRNAs play important roles in the maintenance of ESCs and CSCs

Table 1. miRNAs with Tumor Suppressor or Oncogenic Activities [22, 24, 58]

miRNA	Targeted molecules
Tumor suppressor miRNAs	
let-7	RAS, PRDM1, HMGA2, c-Myc, E2F, cyclin D2, Bcl-XL
miR-30b	Bcl-2, KRAS, PI3KCD,
miR-15/miR-16	Bcl-2, Wt-1, CCND1
miR-34	E2F3, Notch1, CDK4, CDK5, c-Met, BCL-2, SIRT1, HMGA2, p53, E2F3, Bcl-2
miR-17-5p	AIB1, E2F1, p21, BIM
miR-29	MCL-1, TCL-1, DNMT3s, CCND2, Akt2
miR-124	CDK6, STAT3, CCND2
miR-127	Bcl-6
miR-143	Ras, ERK5
miR-145	Mucin1, ERG
miR-181	Colorectal cancer
miR-205	E2F1, LAMC1
miR-375	PDK1, 14-3-3f, AEG-1, IGF1-receptor
miR-31	Integrin alpha5, RhoA, MMP16, Radixin, WAVE3
miR-203	Caveolin 1, LASP1
miR-100	Mcl-2, mTOR, IGF1R, FKBP51
miR-125a-3p	P53
miR-192	Caspase 7, VEGF-A, Bcl-2, Zeb2, PARP
miR-449	p21, p53, Bcl-2,
miR-200c	FAP-1
Oncogenic miRNAs	
miR-21	PTEN, TPM1, PDCD4, maspin, Bax, Bcl-2, Akt,
miR-155	AT1R, TP53INP1, FoxO3a
miR-17-92	Tsp1, CTGF, E2F1, AIB1, TGFBR2, PTEN, RB2, NF-KB, Bim
miR-106a	RBL1/2
miR-373	LATS2
miR-197	ACVR1, TSPAN3, FUS1
miR-221	KIT, p27(Kip1), p57, PTEN, Cx43
miR-222	KIT, p27(Kip1), p57, PTEN, Cx43
miR-372	LATS2
miR-301	FoxO2, BBC3, PTEN, COL2A1
miR-31	Akt, ABCB9, RhoA, radixin, integrin-25
miR-92a	FoxO1, Bim
miR-196a	HOXA5, ING5
miR-181a/b	AC9, PRKCD
miR-141	YAP1

and their transition between self-renewal, proliferation and differentiation. Naturally, miRNAs are often associated with novel therapeutic ideas. Several examples exist, wherein they have already been successfully implemented to break barriers in treatment of various diseases [35]. However, studies have also revealed that dysregulated miRNAs target oncogenes, tumor suppressor genes, and transcription factors (**Table 1**) and inhibition and/or overexpression of these miRNAs affect cell migration, invasion, proliferation, and apoptosis (**Figure 3**). If the recent research reports on microRNAs is anything to go by, then there is much potential for their clinical applications in the context of regenerative medicine and cancer treatment.

Interestingly, natural agents have been reported to modulate the expression of individual miRNAs by a relatively small increment [36, 37]. However, these natural agents have the ability to simultaneously regulate multiple putative tumor suppressor and oncogenic miRNAs (**Table 2**). Although it is yet to be determined whether the combined modulation of miRNAs or targeting one key miRNA has a superior therapeutic effect, emerging scientific evidence suggests that coordinated regulation of multiple miRNAs may result in synergistic tumor growth suppression [38]. Theoretically, co-regulation of multiple miRNAs could minimize unwanted upregulation of oncogenes, while maintaining upregulation of tumor suppressor genes. Thus, use of agents that targets multiple miRNAs could be more effective and safer strategy for cancer treatment and prevention than targeting individual miRNAs.

Cancer stem cells (CSCs)

Enough scientific evidence exists to suggest that the majority of cells in solid tumors are of non-tumorigenic origin. Cancer stem cells (CSCs) have been reported in many human tumors and are proposed to drive tumor initiation, progression maintenance, invasiveness, metastasis, drug resistance, and recurrence. CSCs share a variety of biological properties with normal somatic stem cells such as self-renewal, asymmetric cell division, differentiation, chemoresistance and the expression of specific stem cell genes [39, 40]. The CSC theory, which is based on the concept that cancer might arise from a rare population of cells with

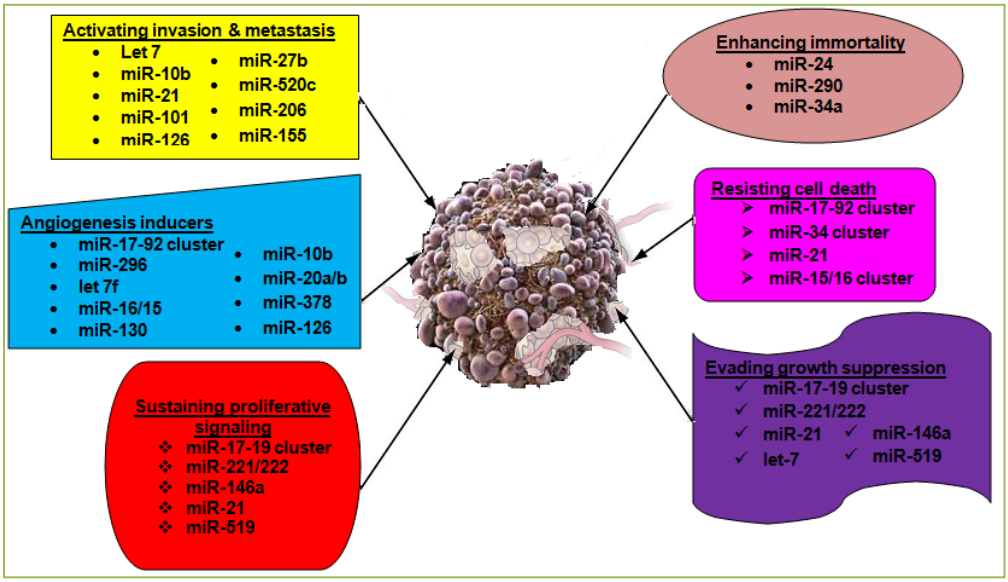

Figure 2. Altered miRNA expression affects signaling pathways to enhance carcinogenesis. Representative miRNA are depicted that have been shown to act as oncogenes or tumor suppressor genes to affect the most common hallmarks of cancer. miRNA, microRNA.

stem cell properties, is generally accepted in the field of cancer biology and research, and in particular with regard to cancer drug discovery. Despite their potential clinical importance, the regulation of CSCs at the molecular level is not well-understood. Normal stem cells and CSCs act via various common signaling pathways that regulate self-renewal activity, including Wnt, Notch, and Sonic Hedgehog, and dysregulation of these pathways is reported to play an important role in tumor initiation and development [41]. A study by Jamieson and colleagues demonstrated that aberrations in the Wnt/β-catenin pathway enhanced self-renewal activity during leukemia stem cell propagation [42]. On the other hand, a study by Korkaya and coworkers reported that the Wnt/β-catenin pathway was involved in the regulation of normal and malignant mammary stem/progenitor cell populations [43]. Accumulating lines of evidence have revealed that Notch pathway is activated in breast, glioblastoma, and colon CSCs [44, 45] while alterations in Hedgehog signaling have been reported in colon, breast, and glioblastoma CSCs [46, 47]. It is now widely accepted that altered stem cell self-renewal is essential for cancer initiation, growth, and relapse and that CSCs play a critical role in cancer cell biology. Therefore, identification of specific CSCs markers may be important in the discovery and development of novel oncology treatment options. So far, the role of CSCs in cancer metastasis and drug resistance is undisputable [48-50]. CSCs are endowed with very tight regulatory framework to ensure their sustenance and overwhelming evidence support the role of epigenetics in regulation of CSCs [51]. Irrespective of the resident CSC theory, it is beyond doubt that the agents capable of targeting CSCs stand a better chance as cancer therapeutic options What's more, CSCs are resistant to conventional treatments and are therefore not only of academic interest, but may also be an important consideration in clinical practice. Therefore, a better understanding of the characteristics of CSCs and the identification of therapeutic agents capable of targeting the CSC population are critical issues.

Modulation of miRNAs by natural agents

A number of reports, including some from our laboratory, have documented the modulation of miRNAs by natural agents [52-56]. Since epigenetic alterations play important roles in aberrant expression of several miRNAs in cancer cells, natural agents are now being investigated for their ability to reverse these changes that will ultimately lead to inhibition of tumor growth, invasiveness and metastasis.

To date, many of the anticancer agents currently used in cancer therapies have been developed from natural products such as plants (vincristine, vinblastine, etoposide, paclitaxel, camptothecin, topotecan, and irinotecan), marine organisms (cytarabine), and microorganisms (dactinomycin, bleomycin, and doxorubicin) [57]. MiRNAs are being considered as attractive targets for cancer prevention and therapy due to their oncogenic or tumor suppressor activities [58] (**Table 1**). Various studies have suggested that the modulation of miRNAs serves as one of the key mechanisms in the anticancer activities of a variety of natural agents (**Table 2**). Additionally, mechanistic studies have demonstrated that they exert their antiproliferative and/or proapoptotic effects to prevent the occurrence and/or spread of various cancers by targeting numerous key elements in intracellular signaling

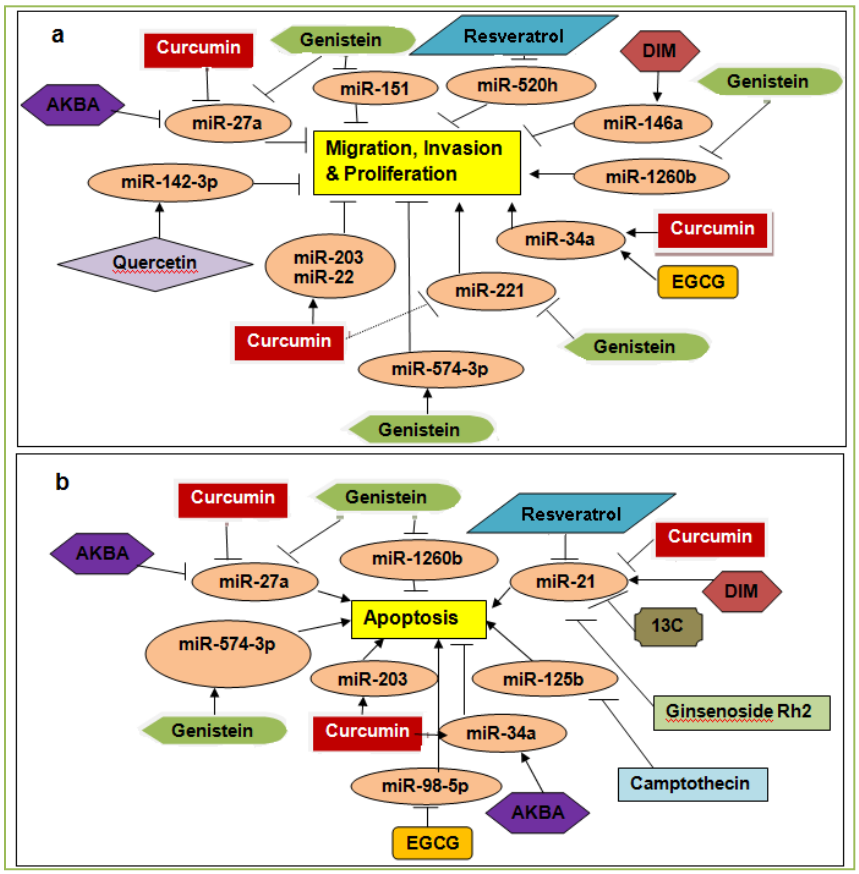

Figure 3. Natural agents alter the expression of miRNAs. Regulation of miRNAs by natural agents and effects of miRNA inhibition or overexpression on (a) cell migration, invasion, proliferation, and (b) apoptosis. AKBA, 3 acetyl-11-keto-β-boswellic acid; DIM, 3,3′-diindolylmethane; EGCG, epigallocatechin-3-gallate; 13C, Indole-3-Carbinol; miR, microRNA.

network involved in carcinogenesis [59]. Here we describe some of the natural agents which are known to regulate miRNA expression in cancer.

Curcumin

Curcumin, the principle curcuminoid and a derivative of the spice turmeric *curcuma longa*, is used as a naturally occurring medicine to treat variety of inflammatory disorders and human cancers [60]. A study by Sun and colleagues reported upregulation of 11 miRNAs and downregulation of 18 miRNAs in curcumin-treated pancreatic cancer cells [61]. They reported that miR-22 was upregulated upon curcumin treatment, and the predicted targets were ERα and transcription factor Sp1, while miR-196, an oncogenic miRNA in gastric cancers, was significantly downregulated after curcumin treatment [61]. Curcumin has been shown to downregulate putative oncogenic miRNAs, such as miR-21 [62, 63], while it upregulates key tumor-suppressor miRNAs, including miR-200 family, let-7 family, miR-185b, and miR-22 [64, 65, 66]. More recently, Toden and colleagues reported that curcumin chemosensitizes colorectal cancer cells to 5-fluorouracil (5FU) by suppression of epithelial–mesenchymal transition (EMT) through upregulation of EMT-suppressive miRNAs in 5-fluorouracil resistant (5FUR) cell lines. Furthermore, they reported that the curcumin-mediated chemosensitization of 5FU-resistant cells can be further controlled through modulation of miR-200c expression [37]. In another study they demonstrated that curcumin and AKBA induced upregulation of miR-34a and downregulation of miR-27a in colorectal cancer cells [36].

A study by Yang *et al*. has shown that curcumin upregulated miR-15a and miR-16 in MCF-7 breast cancer cells which caused an induction of apoptosis [67]. Curcumin has also been shown to induce tumor suppressor miR-186 expression to promote apoptosis in lung cancer [68]. Zhao *et al*. reported that curcumin exerts its cytotoxic effects against SKOV3 ovarian cancer cells largely through upregulation of miR-9 [69]. Another tumor suppressor, miR181b, has been demonstrated to be induced by curcumin, and it inhibits breast cancer metastasis [65]. High levels of miR-221 expression have been correlated with shorter survival in pancreatic cancer patients, suggesting that miR-221 could be

Table 2. Natural agents regulation of miRNAs in cancer. Modulation of miRNA expression by certain natural agents and effect on cancer biology

Natural agent	miRNA	Function	Reference
1. Resveratrol	↑miR-141, miR-663, miR-34a, miR-744, miR-622 and miR-200c ↓miR-17, miR-21, miR-25, miR-92a-2, miR-103-1, and miR-103-2	Invasiveness, EMT, and metastasis	[88-94]
2. EGCG	↑miR-16, miR-210, miR-7-1, miR-34a, and miR-99a ↓miR-21, miR-98-5p, miR-92, miR-93, and miR-106b	Apoptosis, Proliferation, drug resistance	[95-100]
3. Genistein	↑miR-16, miR-574-3p, miR-1296 ↓miR-221, miR-222, miR-27a, miR-151, miR-1260b, miR-223	Apoptosis Growth	[76-87]
4. Curcumin	↑miR-15a, miR-16, miR-34a, miR-186, miR-22, miR-200 family, let-7 family, miR-185b, miR-181a ↓miR-21, miR-221, miR-27a, miR-199a, miR-98, miR-195, miR-510, miR-374,	Apoptosis Metastasis	[36,37, 61-71]
5. Quercetin	↑ let-7 ↓ miR-27a	Growth Apoptosis	[55, 101-104]
6. CPT	↑miR-155, miR-17-5p, and miR-18a ↓ miR-125b	Growth Apoptosis	[108, 109]
7. DIM	↑miR-21, miR-200b, miR-200c, let-7b, let-7c, let-7d, let-7e, and miR-146a ↓miR-200, miR-221, miR-92a	Growth, EMT, drug resistance, invasion, and metastasis	[70,85,86,111, 112]
8. I3C	↓miR-21, miR-31, miR-130a, miR-146b, and miR-377	Proliferation	[110,113, 114]
9. AKBA	↑let-7 family, miR-200 family, miR-34a ↓miR-27a	Apoptosis, proliferation Cell-cycle regulation	[36, 72]
10. Baicalin	↑miR-378, miR-199a-3p, miR-181b ↓miR-23a, miR-294	DNA repair Apoptosis, Proliferation	[56, 73,75]
11. Rh2	↑miRNA-128 ↓miR-21	Proliferation Apoptosis, growth	[115, 116]
12. Sulforaphane	↑miR-200c, miR-140	EMT	[119, 121]
13. ACA	↓miR-23a	Proliferation, apoptosis	[117, 118]
14. Ellagitannins	↑let-7e, miR-370, miR-373, miR-526b ↓let -7(a-d)	Proliferation, apoptosis differentiation	[122, 123]

Abbreviations: I3C: Indole-3-Carbinol; ACA: 1´S-1´-acetoxychavicol acetate; AKBA: 3 acetyl-11-keto-β-boswellic acid; CPT: Camptothecin; DIM: 3,3´-Diindolylmethane; EGCG: Epigallocatechin-3-Gallate; EMT: Epithelial-to-Mesenchymal Transition; miR: microRNA; Rh2: Ginsenoside Rh2.

an oncogenic miRNA [70]. In another study, curcumin treatment resulted in the upregulation of tumor suppressor miR-203 in bladder cancer that led to apoptosis induction and diminished proliferation, migration, and invasion [71]. Importantly, in a study by Zhang and colleagues regarding curcumin and multi-drug resistance, reported that alterations were detected in 342 miRNAs [68]. Curcumin treatment led to significant changes (> 2.5 fold) in various oncogenic and tumor suppressor miRNAs. A key target was miR-186*, which promoted apoptosis in cancer cells. Taken together, these studies provide evidence for the idea that diet-induced miRNAs may play an important role in overcoming drug resistance in cancers.

Boswellic acid

Boswellic acid (3 acetyl-11-keto-β-boswellic acid-AKBA) upregulates the key putative tumor-suppressive miRNAs of the let-7 and miR-200 family in colorectal cancer and the expression of these miRNAs inversely corresponds with tumor size and volume in a xenograft animal model [72]. AKBA suppresses tumor growth by inducing upregulation of tumor-suppressive miR-34a and downregulation of miR-27a in colorectal cancer cells [36]. Curcumin and AKBA acts synergistically to exert antitumorigenic effects in colorectal cancer cells, in both in vitro and in vivo experimental models. Combined bioinformatics and in silico analysis identifies apoptosis, proliferation, and cell-cycle regulatory signaling pathways as key modulators of AKBA-induced anticancer effects. Therefore, regulation of miRNAs appears to be a crucial antitumorigenic mechanism of AKBA and warrants further systematic and comprehensive investigation.

Baicalin

Baicalin alters the expression pattern of miRNAs in ultraviolet radiation B (UVB) treated mice compared to controls [73]. Three miRNAs (miR-378, miR-199a-3p and miR-181b) are downregulated while one miR-23a is upregulated in baicalin treated mice compared with UVB irradiated mice. These miRNAs are predicted to be related to DNA repair signaling pathway. Our recently published data revealed that baicalin inhibited ESCs proliferation with increase of cells in G1-phase and a decrease in S phase [56] (**Figure 4**). Baicalin downregulates proto-oncogenes c-jun and c-fos as well as down-regulation of miR-294 expression

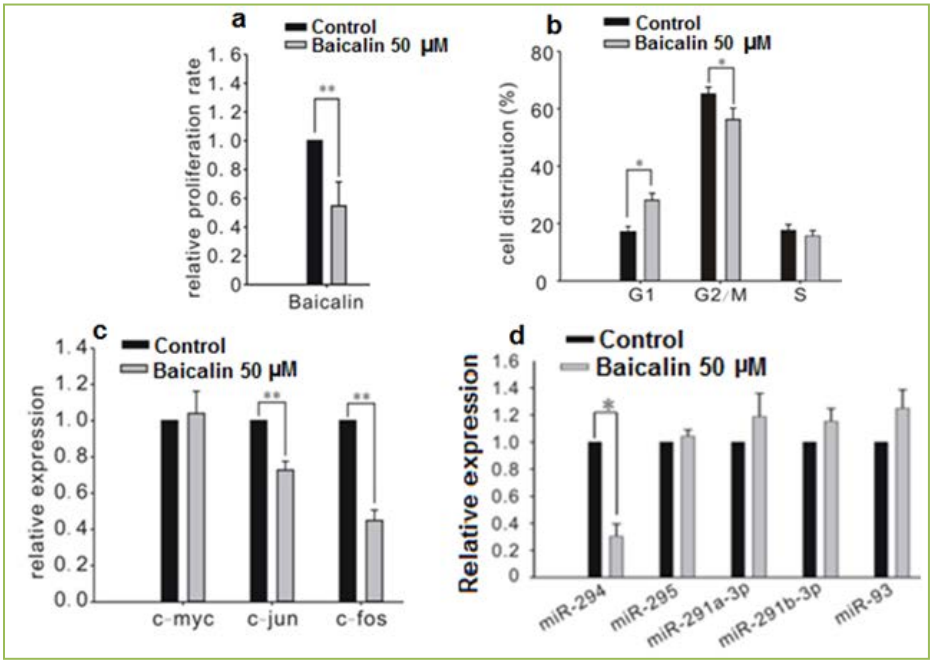

Figure 4. Effects of Baicalin on mESCs proliferation, expression of proto-oncogenes and expression of members of miR-290 cluster. (a) Baicalin 50 μM inhibited the proliferation of mESCs to 0.55 ± 0.04 vs. control ($p<0.01$, n=14). (b) Baicalin administration led to accumulation mESCs in G1and G2/M phases compared to controls ($p<0.05$, n=4). (c) Baicalin 50 μM administration resulted in down-regulation of proto-oncogenes c-jun and c-fos ($p<0.05$, n=5). (d) Baicalin 50 μM treatment led to down-regulation of miR-294 ($p<0.05$, n=4) with no significant effect on the other members of miR-290 cluster ($p>0.05$, n=4). (Reproduced and modified from [56]).

in mESCs while overexpression of miR-294 in mESCs reverses the alterations in the mESC proliferation and the expression of c-jun and c-fos induced by baicalin. Our results are in good agreement with the observations in cancer cells and vascular smooth muscle cells (VSMCs) [74, 75]. Since recent reports have implicated miRNAs in the regulation of proliferation, differentiation and apoptosis in cancer cells and ESCs, it seems possible that miRNAs might also contribute to the cellular mechanisms of decreased proliferation and differentiation and increased apoptosis induced by baicalin in cancer cells. Studies on miRNA modulation by baicalin in cancer cells are limited and therefore more investigations are needed to determine the miRNA regulatory effect of baicalin in ESCs and cancer cells with a view of translating such findings into clinical therapeutic applications.

Genistein

Genistein is an important polyphenol that has shown significant anticancer effects through the regulation of miRNAs. Genistein treatment enhances apoptosis synergistically with miR-16 in human chronic lymphocytic leukemia cells [76]. In prostate cancer, genistein both downregulates miR-221 and miR-222 and restores tumor suppressor gene aplasia Ras homolog member I (ARHI) expression, which ultimately results in anticancer effects [77]. In prostate cancer, genistein inhibits the migration and invasion of PC3 and DU145 cells through downregulating oncogenic miR-151 [78]. Treatment of ovarian and pancreatic cancer cells with genistein causes inhibition of cell growth and migration through suppression of miR-27a [79, 80]. Furthermore, genistein upregulates the tumor suppressor miR-574-3p in prostate cancer cells [81], and exerts its antitumor effect in prostate cancer via downregulation of miR-1260b [82]. Genistein treatment downregulates oncogenic miR-1260b and results in inhibition of Wnt-signaling in renal cancer cells [82].

Additionally, miR-223 expression is downregulated in pancreatic cancer cells after genistein treatment that correlated with cell growth inhibition and induction of apoptosis [83]. Genistein also upregulates miR-146a in pancreatic cancer cells, inhibiting their invasive potential by downregulating EGFR, NFκB, IRAK-1, and MTA-2 [84]. In another study, Li *et al.* reported a differential effect in gemcitabine-resistant versus gemcitabine-sensitive pancreatic cancer cells. They reported that miRNAs of miR-200 and let-7 families were downregulated in gemcitabine-resistant cells versus gemcitabine-sensitive cells, however, isoflavone treatment increased both miR-200 and let-7 family miRNAs by modulating EMT transcription factors, such as vimentin, slug, and ZEB1 [85]. In another study, prostate cancer cells

treated with genistein and the researchers reported that minichromosome maintenance 2 gene (MCM2) was downregulated by miR-1296 and genistein induced the expression of miR-1296 by up to five-fold, along with cell cycle arrest in S-phase [86]. Furthermore, genistein was also investigated in other cancer models, such as human uveal melanoma cells [87]; using both *in vitro* and *in vivo* models, miR-27a was found to be downregulated with concomitant upregulation of its target gene, ZBTB10.

Resveratrol

Resveratrol (3,4′,5-trihydroxystilbene) is a natural phytoalexin in several plants, such as grapes, berries, plums, and peanuts. It has anticancer activities against various cancers including breast cancer, lung cancer, glioma, prostate cancer, colon cancer, and neuroblastoma [88, 89]. It reduces the expression of numerous oncogenic miRNAs, namely, miR-17, miR-21, miR-25, miR-92a-2, miR-103-1, and miR-103-2, in human colon cancer cells [90]. In the same study, tumor suppressor miR-663 levels are restored in human colon cancer cells after treatment of resveratrol. In another study, resveratrol treatment upregulates miR-141 and results in a significant reduction of invasiveness, whereas resveratrol-induced miR-200c expression causes reversal of EMT through downregulation of Zeb1 and upregulation of E-cadherin [91]. The anticancer effect of resveratrol in pancreatic cancer cells is proposed to due to inhibition of oncogenic miR-21 [92]. Moreover, the synergistic antitumor activity of resveratrol and miR-200c has been demonstrated in human lung cancer cells [93]. In colon cancer cells, resveratrol inhibits the cell growth and induces apoptosis through up-regulating miR-34a expression [94].

Epigallocatechin-3-gallate (EGCG)

Epigallocatechin-3-gallate (EGCG) is a polyphenol flavonoid of natural green tea that possesses significant antioxidant and anticancer properties [95]. EGCG increases the expressions of 13 miRNAs including miR-16 and decreases the levels of 48 miRNAs in HepG2 human hepatic cancer cells [96]. EGCG induces apoptosis in hepatocellular carcinoma through enhanced expression of miR-16 [96]. Increased expression of miR-16 results in inhibition of its target antiapoptotic Bcl-2, followed by mitochondrial dysfunction, cytochrome c release, and subsequent apoptosis. EGCG also inhibits the expression of miR-21 followed by repression of androgen receptor (AR) signaling and, consequently, a reduction of prostate cancer cell growth [97]. In lung cancer, EGCG upregulates the expression of miR-210, which leads to the inhibition of proliferation and anchorage-independent growth [98]. EGCG enhances the efficacy of cisplatin through downregulation of miR-98-5p in A549 non-small lung cancer cells [99]. A combination of N-(4-hydroxyphenyl) retinamide and EGCG decreases the expression of oncogenic miRs (miR-92, miR-93, and miR-106b) and enhances the expression of tumor suppressor miRs (miR-7-1, miR-34a, and miR-99a) which results in growth inhibitory effects in human malignant neuroblastoma cells [100]. All of these experiments have indicated that EGCG has the potential to inhibit cancer growth via miRNAs although much more studies are warranted.

Quercetin

Quercetin, a flavonoid found in onions, apples, tea, and red wine, upregulates miR-142-3p in pancreatic ductal adenocarcinoma cells [101]. Indeed, intake of a quercetin-rich diet modulates the expression of 48 unique miRNAs [102]. These miRNAs have been reported to decrease tumor metastasis and invasion (miR-146a/b, 503, and 194), inhibit cell proliferation (miR-125a, 155, let-7 family, 302c, 195, 26a, 503, and 215), induce apoptosis (miR-125a, 605, 26b, let-7g, 34a, 491, and 16), and upregulate tumor suppressor miRNAs (let-7 family, miR-125a, 183, 146a, 98, 19b, 106a, and 381) [102]. Recently, Del Follo-Martinez *et al*. reported that quercetin treatment induced apoptosis in colorectal cancer cells when used along with resveratrol [103]. The underlying mechanism of apoptosis induction was closely related to the downregulation of oncogenic miR-27a [103]. In another study, quercetin, when used with catechins, enhanced the expression of let-7 in pancreatic cancer cells followed by K-ras inhibition and reduction of the advancement of pancreatic cancer [55]. Furthermore, the upregulation of miR-146a, a negative regulator of NF-κB activation, by quercetin protects CCD-180Co colonic myofibroblast cells against ROS [104].

Camptothecin (CPT)

Camptothecin, an alkaloid isolated from bark of Camptotheca acuminata, is a potent chemotherapeutic agent against a variety of tumors [105-108]. CPT reduces the expression of miR-125b significantly, which led to the upregulation of Bak1 and p53 and resulted in apoptosis of human cervical cancer and myelogenous leukemia cells [107]. In a recent study, camptothecin inhibits HIF-1α by enhancing the levels of miR-155, miR-17-5p, and miR-18a in HeLa cells [109].

Indole-3-Carbinol (I3C) and Diindolylmethane (DIM)

Diindolylmethane is an active compound that is generated in the stomach through the metabolic conversion of Indole-3-carbinol (I3C), present in cruciferous vegetables such as cabbage, broccoli, cauliflower, kale, radish, turnip,

and brussels sprouts [110]. DIM regulates the expression of numerous miRNAs involved in cancer development and progression. It induces the expression of certain miRNAs, such as miR-200 and let-7 families, that leads to the reversal of EMT and enhanced chemosensitivity in gemcitabine-resistant pancreatic cancer cells [84, 85]. DIM also induces the expression of miR-146a, which reduces pancreatic cancer cell invasion via inhibition of metastasis-associated protein 2 (MTA-2), interleukin-1 receptor-associated kinase 1 (IRAK-1), and NFκB [84]. Jin observed that DIM inhibited breast cancer cell growth by enhancing the expression of miR-21 which led to the degradation of its target Cdc25A [111]. Formulated 3,3-diindolylmethane (BR-DIM) is capable of downregulating miR-221, resulting in growth inhibition of pancreatic cancer cells and patients with high expression of miR-221 are reported to have a relatively shorter survival compared to those with lower expression[70]. DIM can downregulate miR-92a which is associated with receptor activator of nuclear factor-*κ*B ligand (RANKL) signalling, EMT, and cancer progression to inhibit differentiation of osteoclasts and osteoblasts in prostate cancer metastasis [112]. Remarkably, upregulation of miR-21, miR-31, miR-130a, miR-146b, and miR-377 observed in vinyl carbamate-induced lung cancer in mice is reversed by I3C [113]. PTEN, PDCD4, and reversion-inducing-cysteine-rich protein with Kazal motifs (RECK) are identified as potential targets of miR-21 [113]. Recently, a study by Paik and colleagues reported that 13C downregulated miR-21 in Panc-1 pancreatic carcinoma cells. Overexpression of miR-21 negated I3C-induced sensitivity towards gemcitabine and reduced the expression of its target, PDCD4, which was upregulated by I3C [114]. Taken together, these encouraging results show that DIM and I3C could be harnessed as potential anticancer therapeutic agents.

Ginsenoside Rh2

Ginsenoside Rh2 is a biologically active phytochemical extracted from Ginseng, a commonly used alternative drug taken orally in traditional herbal medicines in China, Korea, Japan and some Western countries [115]. It is a triterpene saponin, consisting of a steroid nucleus and a sugar moiety [115]. Ginsenoside Rh2 altered miRNA expression in human glioma U251 cells, including up-regulating 14 and down-regulating 12 miRNAs. Ginsenoside Rh2 also exerts its anti-proliferative effect in human glioma cells in part by up-regulation of miRNA-128 expression [116], while down-regulating miR-21 which leads to glioma cell apoptosis and cell growth inhibition, reduced invasiveness and suppressed tumorigenicity [116]. Further studies are needed to investigate the molecular mechanism of Rh2-induced down-regulation of miR-21 as an anti-proliferative effect in cancer cells and to firmly establish these study findings so as to expedite translation of such findings into efficacious clinical applications.

1′S-1′-acetoxychavicol acetate (ACA)

Recently, Phuah and colleagues [117] reported that a total of 25 miRNAs were found to be significantly differentially expressed following treatment with 1′S-1′-acetoxychavicol acetate (ACA), a natural compound isolated from the wild ginger, Alpinia conchigera, and/or cisplatin on Ca Ski and HeLa cervical carcinoma cells. These included miR-138, miR-210, and miR-744 with their predicted targets involved in signaling pathways regulating apoptosis and cell cycle progression [117]. Another study reported that ACA downregulated miR-23a in HN4 head and neck Squamous cells and its inhibition suppressed cell proliferation and induced apoptosis, with PTEN confirmed as its target [118].

Sulforaphane

Sulforaphane, an isothiocyanate, is derived from cruciferous vegetables such as broccoli and broccoli sprouts. It upregulates 15 miRNAs (miR-372, miR-342-3p, miR-486-5p, miR-9, miR-9, miR-145, miR-146a, miR-629, miR-505, miR-758, miR-30a, miR-27b, miR-135b, miR-27b, and miR-23b) while downregulating 3 miRNAs (miR-633, miR-155, and miR-106a) in NCM460 and NCM356 normal colon epithelial cells [119]. In sulforaphane-treated T24 bladder cancer cells, miR-200c is upregulated, leading to inhibition of EMT and metastasis. Downregulation and overexpression of miR-200c reverses and enhanced ZEB1 repression and E-cadherin induction by sulforaphane, respectively [120]. MiR-140 is upregulated following sulforaphane treatment in MCF10DCIS and MDA-MB-231 breast cancer cells. Both SOX9 and aldehyde dehydrogenase 1 (ALDH1) are also identified as targets of miR-140 and miR-140 overexpression downregulated the protein levels in both targets [121]. Recently, sulforaphane was reported to complement with quercetin and catechins in elimination of advanced pancreatic cancer by miR-let-7 induction and K-ras inhibition [55]. Further research is warranted to firmly establish these research findings and explore the possibility of the use of sulforaphane as a cancer therapeutic adjuvant option.

Ellagitannins

Ellagitannins are polymeric polyphenols abundant in strawberries, raspberries, almonds, walnuts, and various other fruits and nuts. These are polyesters of ellagic acid and a sugar moiety and upon hydrolysis release ellagic acid. Ellagitannins have been reported to exhibit anti-oxidant,

radical scavenging, antiviral, antimicrobial, anti-mutagenic, anti-inflammatory, anti-tumor promoting and immunomodulatory properties [122]. Ellagitannins modulate transcription factors and signaling pathways which inhibit cancer cells proliferation and induce their apoptosis. For example, liver cancer cells exposed to ellagitannin BJA3121, isolated from a plant *Balanophora japonica* exhibited cell growth inhibition and alteration in the expression of several miRNAs. Using a dose- and time-dependent strategy, 17 miRNAs were found to be upregulated and 8 miRNAs were downregulated following treatment of HepG2 cells. These included upregulation of miR-let-7e, miR-370, miR-373 and miR-526b and downregulation of let-7a, let-7c, let-7d which correlates with genes involved in cell differentiation and proliferation [123]. Prediction software and functional analyses identified likely targets with roles in cell proliferation and differentiation. However, the precise mechanisms await further studies.

Role of nutritive natural agents in the regulation of miRNAs

Studies have shown that dietary components such as folate, Vitamin D and retinoids could modulate miRNA expression then exert inhibitory effects on cancer [124]. Indeed, folic acid has been reported to down-regulate miR-10a [125], suggesting the regulatory role of dietary factors on miRNA. Hepatocellular carcinoma in rats fed a folate-deficient diet for 54 weeks was associated with upregulation of several miRNAs, including miR-21, and downregulation of liver-specific miR-122. Folate treatment increased suppressor miR-122 levels, and was associated with inhibition of tumorigenesis, suggesting a potential chemoprevention paradigm affecting miRNAs [126]. On the contrary, vitamin E deficiency in rats decreased tumor suppressor miRNAs in the liver. Vitamin E has also has been reported to modulate lipid metabolism, inflammation, and other cancer-associated pathways by reducing the expression of miR-122 and miR-125b [127].

Vitamin D has long been considered as an essential nutrient for human health and evidence from epidemiologic and experimental studies have indicated that higher intakes of vitamin D from food and/or supplements leads to higher blood levels of vitamin D, which are highly associated with reduced risks of certain cancers [128, 129]. Vitamin D and its metabolites, 1,25-dihydroxyvitamin D_3 (1, $25D_3$) and 25-hydroxyvitamin D_3 ($25(OH)D_3$), regulate miRNA profiles in different cancers. In one study, human myeloid leukemia cells treated with $1,25D_3$ displayed downregulation of miR-181a and miR-181b and enhanced expression of p27Kip1 and p21Cip1, as well as G1 cell cycle arrest [128]. It has been reported that $25(OH)D_3$ could modulate p53 and PCNA levels, alter miR-182 expression, and contribute to a protective role against cellular stress in breast epithelial cells [129]. Importantly, cancer chemopreventive effects of vitamin D and its metabolites are thought to be mediated via binding with its receptor (VDR). MiR-125b is identified as having a potential sequence match in the 3'-UTR region of human VDR mRNA, suggesting a pathway for targeted therapy via VDR downregulation in human cancers [130]. Nonetheless, the precise role of vitamin D on the CSC-related miRNAs is not yet clear. Therefore, further investigations are required to elucidate the role of vitamin D in the regulation of CSC characteristics and miRNAs in the development and progression of cancer.

Retinoic acid (RA) is an active metabolite of vitamin A, it is involved in cellular differentiation by modulating miRNA expression in various cells, including acute promyelocytic leukemia [131] and neuroblastoma cell lines [132]. In cells derived from acute promyelocytic leukemia patients after incubation with 100 nmol/L all-trans retiRA, eight miRNA were upregulated (miR-15a, miR-15b, miR-16–1, let-7a-3, let-7c, let-7d, miR-223, miR-342, and miR-107) and one was downregulated (miR-181b) [131]. It is proved that RA upregulates let-7a-3 by inducing NF-kB that binds to the promoter of the let-7a-3 gene. Furthermore, all-trans-RA downregulates K-Ras and Bcl2 and correlates with the activation of known miRNA regulators of those proteins, let-7a and miR-15a/miR-16–1, respectively [131]. Taken together, these results reveal that miRNAs could be useful as biomarkers for cancer prevention, treatment, diagnosis and prognosis and as such assessing nutritional status in dietary intervention studies could be of great value.

A study by Davidson *et al*. evaluated the chemopreventive effects of n-3-Polyunsaturated fatty acids (n-3 PUFAs) on azoxymethane-induced colon cancer in rats [133]. Carcinogen significantly downregulated of five known tumor suppressor miRNAs, which were reversed upon exposure to n-3 PUFA[133]. Based on transfection experiments *in vitro*, tumor suppressor protein, PTEN was found to be targeted by oncogenic miR-21 in human colon cancer cells. Additionally, beta site amyloid precursor protein-cleaving enzyme (BACE-1) was targeted by tumor suppressor miR-107 and was downregulated in carcinogen-induced tumor tissues compared with normal colonic mucosa [133]. The chemoprotective role of dietary n-3 PUFAs by modulating miRNA was evidenced in this study. Similarly, short chain fatty acids which inhibit HDAC activity, such as butyrate, are also reported to alter miRNA patterns regulating endodermal differentiation mechanisms, as studied in human embryonic stem cells [134].

Other natural agents

A study by Wang and colleagues reported that **Ursolic acid**, a pentacyclic triterpene acid found in medicinal herbs such as *Oldenlandia diffusa* and *Radix actinidiae*, induced apoptosis in U251 glioblastoma cells by downregulating miR-21 and inducing the expression of PDCD4, a target of miR-21. Overexpression of miR-21 suppressed the Ursolic acid-induced expression of PDCD4 [135]. **Garcinol**, a polyisoprenylated benzophenone derivative obtained from *Garcinia indica* extracts, reverses EMT in MDA-MB-231 and BT-549 breast cancer cells as well as in xenograft mouse model through upregulation of let-7a, let-7e, let-7f, miR-200b, and miR-200c. Additionally, inhibition of miR-200a, miR-200b, and miR-200c attenuates the garcinol-mediated inhibition of invasion [54]. **Matrine**, an alkaloid isolated from Sophora flavescens, downregulates miR-21 to induce overexpression of PTEN and inactivate Akt, leading to cell cycle arrest and apoptosis in MCF-7 breast cancer cells [136]. More recently, a study by Cufi´ *et al*., reported that a water-soluble formulation of the flavolignan **silibinin**, the bioactive constituent of silymarin isolated from the dried fruits of the milk thistle, *Silybum marianum* plant [137], was able to reverse the epithelial-to-mesenchymal transition (EMT)-related high miR-21/low miR-200c microRNA signature and repressed the mesenchymal markers SNAIL, ZEB, and N-cadherin observed in erlotinib-refractory non-small cell lung cancer (NSCLC) tumors [138]. Isothiocyanates, such as **phenethyl isothiocyanate** (PEITC) has been proposed to be a useful chemopreventive agent that can inhibit carcinogenic process. In one study, PEITC strongly counter-regulated the expression of majority of miRNAs downregulated by cigarette smoke which included; miR-125b, miR-26a, miR-146-pre, let-7a, let-7c, miR-192, miR-222-pre, miR-99 and miR-123 designated for TGF-β expression, NF-κB activation, Ras activation, cell proliferation, apoptosis and angiogenesis [139]. On the other hand, **Selenium** deficiency increases cancer risk. A study by Sarveswaran and colleagues has demonstrated that selenium activated p53 and increased its targets in the miR-34 family [140]. They reported that specific members of miR-34 family, miR-34b and miR-34c, but not miR-34a, increased significantly in prostate cancer cells treated with sodium selenite (an inorganic form of selenium). However, it is necessary to test these effects on a case-by-case basis, including their metabolites because of the toxicity concerns associated with inorganic and some organic forms of selenium [141- 143].

Conclusion and Future Perspective

Based on the studies mentioned in this review, it is clear that natural agents modulate miRNAs leading to cancer prevention. MiRNAs have been characterized as the biomarkers for diagnosis and prognosis, markers of risk stratification and targets for cancer therapeutics, thus becoming attractive targets for cancer therapy and other therapies. To that end, natural agents could target miRNAs, which in turn could enhance the efficacy of conventional cancer therapies. Thus, targeting miRNAs by natural agents could open newer avenues in the treatment of cancer and in the ESCs as research tools. Natural agents display an inimitable ability in modification of cancer biology by modulating the expression of miRNAs through a variety of mechanisms, namely, epigenetic, transcriptional, and miRNA processing. It is our perspectives that natural agents could alter miRNA expression profiles, therefore inhibiting cancer growth, inducing apoptosis, reversing EMT phenotype, and increasing drug sensitivity. Consequently, regulation of miRNAs by natural agents could be a novel strategy toward designing combination approaches with conventional therapies for the treatment and prevention of tumor recurrence and may ultimately lead to successful treatment outcome of patients diagnosed with cancers. Despite the promising and good results of anticancer activities by natural agents, there are some hurdles such as low bioavailability. To this end, different approaches will be required to overcome these caveats including chemical modification, synthetic formulations, delivery by nanoparticles, amongst others. Thus, it is hoped that these new strategies would prevent tumor recurrence and resistance towards conventional therapies, leading to improvement in the overall response and survival of cancer patients.

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Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' contributions

MJ conceived of the study and drafted the manuscript. ZY contributed to the previous study and some parts of the manuscript. HJ and LH participated in the study design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

List of abbreviations

ACA: 1´S-1´-acetoxychavicol acetate; AKBA: 3 acetyl-11-keto-β-boswellic acid; CPT: Camptothecin; CSCs: cancer stem cells; DGCR8: Di George syndrome critical region gene 8; DIM: 3,3´-diindolylmethane; EGCG,

epigallocatechin-3-gallate; EMT: Epithelial-to-Mesenchymal Transition; I3C: Indole-3-Carbinol; miRNAsmicroRNAs; RISC: RNA-induced silencing complex; TCM: Traditional Chinese Medicine; mESCs: mouse embryonic stem cells.

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