Current state of phenolic and terpenoidal dietary factors and natural products as non-coding RNA/microRNA modulators for improved cancer therapy and prevention

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ABSTRACT

The epigenetic regulation of cancer cells by small non-coding RNA molecules, the microRNAs (miRNAs), has raised particular interest in the field of oncology. These miRNAs play crucial roles concerning pathogenic properties of cancer cells and the sensitivity of cancer cells towards anticancer drugs. Certain miRNAs are responsible for an enhanced activity of drugs, while others lead to the formation of tumor resistance. In addition, miRNAs regulate survival and proliferation of cancer cells, in particular of cancer stem-like cells (CSCs), that are especially drug-resistant and, thus, cause tumor relapse in many cases. Various small molecule compounds were discovered that target miRNAs that are known to modulate tumor aggressiveness and drug resistance. This review comprises the effects of naturally occurring small molecules (phenolic compounds and terpenoids) on miRNAs involved in cancer diseases.
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1. Introduction

The investigation of the role of microRNAs (miRNAs), short and highly conserved non-coding RNAs of 22-23 nucleotides, for various diseases has risen distinctly over the last years. At the moment, there are more than two thousand miRNAs that regulate about one-third of all human genes [1]. MiRNAs are involved in the regulation of processes such as proliferation, apoptosis, and differentiation of cells [2]. Concerning cancer, miRNAs can exert either tumor suppressor or oncogenic activities [1]. Characteristic patterns of miRNA expression were observed from certain tumor tissues and, thus, miRNAs can also feature valuable diagnostic and prognostic factors [3–7]. In addition, miRNAs play a crucial role for the formation and survival of cancer stem-like cells (CSCs) [8,9]. Epithelial-to-mesenchymal transition (EMT) of cancer cells is regulated by miRNAs which, thus, play a crucial role for the formation of metastases [10,11].

Mature miRNAs bind to target messenger RNAs (mRNAs) and suppress their translation [12]. The biosynthesis of miRNAs generally starts with the transcription of miRNA genes by RNA polymerase II thus generating precursor miRNAs (pri-mRNAs) of several kilobases [13]. Then, the microprocessor complex including the RNase III enzyme Drosha and DGCR8 processes these pri-mRNAs into pre-mRNAs of 65-70 nucleotides that form hairpin structures in the nucleus [13,14]. These pre-miRNAs are transported from the nucleus to the cytoplasm via the transporter Exportin-5 in a Ran-GTPase dependent way [15–17]. In the cytoplasm, the pre-miRNAs are processed by the Dicer-TRBP (tar binding protein) complex leading to double-stranded RNAs which comprise the mature miRNA and its complementary strand [1,15–17]. After separation from the complementary strand, the mature miRNA binds to the AGO2 (Argonaut 2) protein which recruits further proteins forming miRISC (miRNA-induced silencing complex) [18]. MiRISC is able to bind to target mRNAs leading either to a block of translation or to the degradation of the target mRNAs by miRISC. The seed region of the miRNA (nucleotides 2-7 of the 5'-end of the miRNA) binds to the complementary 3'-untranslated regions (UTR) of target mRNAs leading to inhibition of mRNA translation [9,19,20]. Aside negative regulation of mRNA translation, certain miRNAs were also found to promote mRNA translation by recruitment of

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proteins to the AU-rich elements of mRNA or by interference with translation inhibiting proteins [21,22].

It was observed that single miRNAs can target various genes while dysregulation of tumor suppressor or oncogenic miRNAs can be found in many human cancer types [23,24]. Thus, miRNAs with effects on carcinogenesis, cell proliferation and differentiation, apoptosis, and on the formation of metastasis and drug resistance feature a valuable target for the design of potent anticancer drugs [25—27]. The application of accurate miRNAs (either as mimics or as antagomirs) in therapy is limited due to the low cell permeability and the facile degradation of RNA molecules, however, liposomal formulations such as MRX34 of the tumor suppressor miRNA-34a (Mirnarx Therapeutics) revealed sufficient stability and cell delivery of the anti-cancer active miRNA leading to the initiation of phase I clinical trials with MRX34 [18]. Nevertheless, dietary factors and natural products are easily obtained from natural sources and, thus, usually provide a rich supply of low-cost, safe and easily available miRNA-modulatory drug candidates. Suitable anticancer drugs from this pool of anticancer active dietary factors and natural products should either inhibit the activity of oncogenic miRNAs or promote the activity of tumor suppressor miRNAs. This review provides an overview of anticancer active natural products (phenols, terpenes) and their manifold interactions with miRNAs involved in cancer diseases.

2. Classification of miRNAs as tumor suppressors or oncogenes

2.1. Tumor suppressing miRNAs

Let-7 features one of the most prominent tumor suppressing miRNA families, and let-7 miRNAs are distinctly downregulated or even completely lost in certain cancer types [28]. A connection between let-7 and K-Ras mutation was observed and restored let-7 led to significant tumor growth inhibition in K-Ras lung cancer models [29,30]. Downregulation of let-7 was shown for breast, colon, lung and pancreas carcinomas and correlated with worse prognosis in lung cancer patients [28,29,31,32]. The first identified tumor suppressing microRNAs were miR-15 and miR-16 in CLL (chronic lymphocytic leukemia) cells [33]. Increased levels of miR-15a and miR-16-1 induced apoptosis while high levels of the anti-apoptotic Bcl-2 protein led to reduced concentrations of miR-15a and miR-16-1 [34]. Restored miR-16 exhibited growth inhibition in prostate cancer cells [35]. In addition, miR-15 and miR-16 sensitized multidrug-resistant gastric cancer cells to chemotherapy [36]. MiR-34 is another important tumor suppressor that attacks tumor-initiating pancreas cancer cells and leads to apoptosis, cell-cycle arrest, and anti-angiogenesis [37—39]. Singh and coworkers disclosed the tumor suppressing effects of miR-150 in pancreas cancer cells via repression of the oncoprotein MUC4 [40]. In mixed lineage leukemia cells (MLL) miR-495 was suppressed and restoration of this miRNA led to inhibition of leukemia cell growth both in vitro and in vivo [41]. Further examples of tumor suppressor miRNAs with effects on hepatoma and pancreas cancer feature miR-203 and miR-451 [42—45]. Further to this, there are several miRNAs which explicitly suppress metastasis formation. In breast cancer models, the expression of miRNAs such as miR-126, miR-206, and miR-335 reduced bone and lung metastasis formation [46]. MiR-126 also inhibited the migration and invasion of prostate cancer cells [47]. In lung cancer, miR-126 and miR-183 likewise blocked metastasis formation [48,49].

2.2. Oncogenic miRNAs

Several oncogenic miRNAs (OncomiRs) were identified which are overexpressed in many cancer types due to gene amplification or upregulated miRNA gene expression [50]. These miRNAs either block tumor suppressor gene expression or regulate epigenetically the expression of pathogenic genes (oncogenes) [51]. MiR-21 features a prominent example of an oncogenic miRNA which inhibited apoptosis in glioblastoma cells [52]. A connection with the anti-apoptotic Bcl-2 protein was observed in breast cancer cells and down-regulation of Bcl-2 occurred after suppression of miR-21 [53]. In pancreas cancer cells, oncogenic miR-27a was overexpressed and targeted the tumor suppressor Sprouty2 [54]. High levels of miR-424-5p in pancreas cancer cells blocked apoptosis and increased cell proliferation via SOCS6 suppression [55]. Another important OncomiR is miR-155 that promoted the proliferation of triple-negative breast cancers and represents a marker of bad prognosis for pancreas cancer patients [56,57]. Various cancers revealed an overexpression of oncogenic miR-155 [57—59]. The miR-17-92 cluster plays an oncogenic role in various tumor diseases and upregulation of the miR-17-92 cluster correlated with increased tumor formation and angiogenesis [60—62]. B-cell lymphoma models exhibited stronger c-myc-dependent tumor growth upon expression of the miR-17-92 cluster [63]. The miRNA miR-10b was upregulated in breast cancer cells and increased migration, invasion and metastasis formation of breast cancer cells [64]. In addition, miR-10b was a marker for bad prognosis in primary breast carcinoma [64]. The miRNAs miR-373 and miR-520c enhanced the migration and invasion of cancer cells by affection of CD44 expression [65]. The metastatic potential of prostate cancer cells was likewise increased by miR-373 and miR-520c [66]. Breast cancer cells were able to form metastases in mice because of miR-373 and miR-520c overexpression [65]. In addition, clinical samples of breast cancer metastases revealed high miR-373 levels [65]. Various miRNAs contribute to drug resistance in cancer cells. Overexpression of miR-221 and miR-222 led to tamoxifen resistance in breast cancer cells and to TRAIL (tumor necrotic factor-related apoptosis-inducing ligand) resistance in non-small cell lung cancer cells (NSCLC) [67,68]. The cisplatin resistance of ovarian cancer cells correlated with increased miR-214 levels targeting PTEN [69]. The effects of dietary and natural phenolic compounds and terpenoids on these miRNAs as well as on further specific miRNA examples are discussed in the following chapter. A short list of microRNAs with significant oncogenic or tumor suppressing activities in the four main solid tumor diseases of Western peoples [i.e., lung cancer, colorectal cancer, prostate cancer (men), and breast cancer (women)] is given in Table 1 [70—73].

3. Dietary compounds and natural products (phenols and terpenoids) with effects on miRNA expression and activity

3.1. Phenolic compounds

3.1.1. Curcumin and curcuminoids

Curcumin is a phytochemical compound isolated from the rhizomes of turmeric (Curcuma longa, haldi) [74]. Turmeric has been applied as a spice for Asian dishes and as a drug in traditional Indian (Ayurveda) and Chinese (TCM) medicine for centuries. Structurally, curcumin is an α,β-unsaturated β-diketone (diferuloylmethane) that shows keto-enol-tautomerism (Fig. 1) [74]. Curcumin has been thoroughly investigated as an anti-inflammatory and anticancer agent and has already undergone several clinical trials [75]. Curcumin features a pleiotropic agent and targets NF-κB (nuclear factor-κB), Akt (protein kinase B) signaling, Wnt signaling, STAT-3 (signal transducers and activators of transcription-3), COX-2 (cyclooxygenase 2), proteasome, MMP (matrix metalloproteinase), etc. [74]. It also exhibited various effects on miRNAs, which contribute to its sound anticancer activity [75]. In MCF-7 breast cancer cells, curcumin induced the expression

Table 1
A selection of important microRNAs as tumor suppressors or oncogenes in breast cancer, prostate cancer, colorectal cancer and lung cancer diseases.

Compound	Tumor suppressors	Oncogenes
Breast cancer	miR-31, miR-125b, miR-126, miR-146b, miR-200, miR-205, miR-206, miR-335	miR-10b, miR-21, miR-155, miR-373, miR-520c
Prostate cancer	let-7c, miR-15, miR-16, miR-29b, miR-125b, miR-126, miR-143, miR-145, miR-205, miR-331-3p	miR-20a, miR-21, miR-27a, miR-107, miR-141, miR-221, miR-375
Colorectal cancer	miR-1, miR-17-5p, miR-29a, miR-106a, miR-125b, miR-133b, miR-143, miR-144, miR-145, miR-150, miR-195, miR-203, miR-206, miR-345, mir-365, miR-378	miR-9, miR-10b, miR-21, miR-31, miR-92a, miR-124, miR-135a/b, miR-139-5p, miR-141, miR-155, miR-181a, miR-183, miR-185, miR-200c, miR-215, miR-219-1, miR-335, miR-372, miR-608
Lung cancer	let-7 family, miR-7, miR-126, miR-145, miR-183	miR-17-92 cluster, miR-31, miR-146b, miR-155, miR-221, miR-222, miR-630
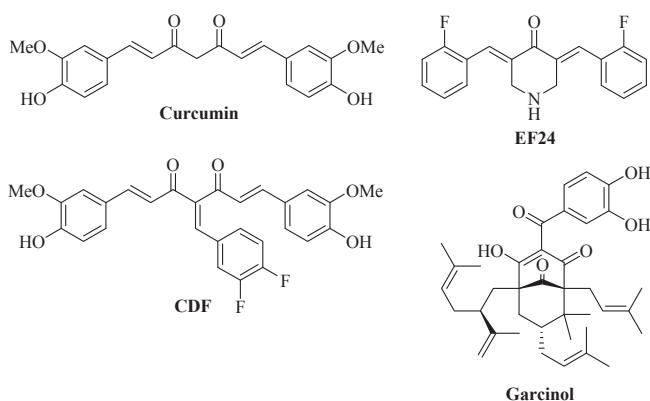
Fig. 1. Chemical structures of curcumin, of the curcuminoids CDF and EF24 and of garcinol.

of the tumor suppressors miR-15a and miR-16 and, thus, suppressed the anti-apoptotic Bcl-2 protein [76]. These miRNAs were also upregulated in K-562 and HL-60 leukemia cells upon treatment with curcumin and WT1 (Wilm's Tumor 1) was identified as a target of miR-15a and miR-16 here [77]. Curcumin also activated the promoter of the miR-203 tumor suppressor gene (by hypomethylation) leading to the overexpression of miR-203 and curcumin-treated bladder cancer cells showed reduced levels of miR-203 targets, the protein kinases Akt and Src, as well as increased apoptosis and decreased proliferation and invasion [78]. Curcumin enhanced the expression of miR-22 in Y79 retinoblastoma cells leading to increased cell growth and migration inhibition via the miR-22 target Erbb3 [79]. In triple-negative breast cancer cells (MDA-MB-231), curcumin induced overexpression of miR-181b leading to inhibition of the formation of MMPs (matrix metalloproteinases) and downregulation of the chemokines CXCL1 and CXCL2 (chemokine C-X-C motif ligand) [80]. These events led to reduced invasion and metastasis formation [76]. Overexpression of miR-9 was observed in ovarian cancer cells (SKOV3) after treatment with curcumin leading to enhanced cytotoxicity [81]. A curcumin diet given to mice suffering from B78H1 murine melanoma revealed distinct tumor regression and a huge overexpression of the murine miRNA mmu-miR-205-5p (135-fold higher expression) in the tumors of curcumin-fed mice [82]. The miRNA miR-205-5p reversed EMT and was downregulated in metastatic melanomas [83,84]. Curcumin blocked pancreatic cancer cell growth and invasion via induction of miR-7 expression associated with suppression of SET8 expression [85]. In NSCLC cells, curcumin-induced apoptosis was correlated with the curcumin-mediated upregulation of the tumor suppressors miR-192-5p and miR-215 in a p53-dependent way leading to down-regulation of XIAP (X-linked inhibitor of apoptosis) [86]. A major drawback of curcumin is its low bioavailability and aqueous solubility, thus, dendrosomal curcumin formulations were prepared which exhibited improved properties

[87]. Indeed, dendrosomal curcumin increased the expression of miR-145 in glioblastoma cells (U87MG) leading to tumor cell growth inhibition via miR-145-mediated suppression of genes involved in the formation of cancer stemness properties such as Nanog, OCT4A (octamer binding protein 4), OCT4B1, and SOX-2 (SRY-box 2) [87]. Dendrosomal curcumin also induced miR-29a and miR-185 expression in hepatocellular carcinoma (HCC) cells associated with suppression of the DNA-methylases DNMT1, DNMT3A and DNMT3b leading to hypomethylation of the MEG3 promoter and increased expression of the tumor suppressing long non-coding RNA MEG3 [88].

Curcumin reduced the expression of the oncogenic miR-21 in colon cancer cells (RKO, HCT-116) leading to reduced tumor growth and metastasis formation by enhanced expression of the miR-21 target PDCD4 (programmed cell death protein 4) [89]. In addition, curcumin downregulated miR-17-5p, miR-20a, and miR-27a (targeting SP repressors, zinc finger and BTB-domain proteins such as ZBTB4/10) in colon cancer cells (RKO, SW480) leading to increased growth inhibition [90]. MiR-21 was suppressed in A549 NSCLC cells after treatment with curcumin as well, followed by activation of the miR-21 target PTEN (phosphatase and tensin homolog) [91]. In human esophageal cancer cells (TE-7), curcumin induced apoptosis and cell cycle arrest via suppression of miR-21 and miR-34a, while the tumor suppressor let-7 was induced by curcumin in these cancer cells [92]. In addition, curcumin successfully inhibited lung cancer cell proliferation (both A549 wt and A549/DDP multidrug resistant cells) and induced apoptosis by downregulation of oncogenic miR-186* which targets caspase-10 [93,94]. Interestingly, there's conflicting data about the role of miR-200 concerning curcumin treatment. In hepatoma cells (HepG2, HepJ5), overexpression of miR-200a and miR-200b led to enhanced curcumin resistance via increased anti-apoptotic Bcl-2 levels and decreased pro-apoptotic Bad and Bax levels [95]. In contrast to that, gemcitabine-resistant pancreas cancer cells (MiaPaCa-E, MiaPaCa-M) showed decreased levels of miR-200b/c while after treatment with curcumin the levels of miR-200b and miR-200c were increased in these cells [96]. Modulation of miR-200c expression (upregulation) also played a role for the curcumin-induced sensitization of colon cancer cells to the approved anticancer drug 5-fluorouracil (5FU) [97]. In prostate cancer cells (PC3), curcumin suppressed oncogenic miR-208 in a dose-dependent way, and, thus, induced the expression of the cell cycle inhibitor and miR-208 target CDKN1A leading to prostate tumor cell growth inhibition [98].

Due to the impressive biological activities of curcumin, the preparation of curcumin derivatives (curcuminoids) with improved properties has become a valuable strategy to obtain sound anticancer drugs. In particular, fluoro-derivatives of curcumin have shown improved anticancer activity when compared with their parent drug curcumin. A remarkable semisynthetic curcuminoid is CDF, the Knoevenagel condensation product of curcumin and 3,4-difluorobenzaldehyde (Fig. 1) [99]. CDF exhibited much higher anticancer activity than curcumin and accumulated in pancreas

tissue making it an interesting drug candidate for pancreas cancer diseases [96,98,100]. CDF was able to re-sensitize drug-resistant pancreatic cancer cells to gemcitabine and enhanced the expression of tumor suppressor miRNAs (miR-200) while it reduced the levels of oncogenic miR-21 leading to PTEN upregulation [96,101]. Under hypoxic conditions, prostate cancer cells upregulate miR-21, however, after treatment with CDF miR-21 expression and tumor growth was efficiently reduced [102]. The hypoxia-mediated aggressiveness of pancreas cancer cells was also related to increased expression of miR-21 and miR-210, and treatment with CDF significantly reduced the expression of miR-21 and miR-210 *in vitro* and *in vivo* [103]. In addition, CDF reduced miR-21 levels and restored PTEN expression in colon cancer cells, while expression of the tumor suppressor miR-34 was induced by CDF in colon cancer [104,105]. CDF was also able to modulate miRNAs targeting matrix metalloproteinases (MMPs) which play a crucial role for the invasion competence of cancers. MiR-874 was upregulated by CDF in non-small cell lung cancer cells which led to MMP-2 inhibition [106]. Oncogenic miR-221 was downregulated by CDF in pancreas cancer cells as well, and CDF inhibited proliferation and migration of pancreas cancer cells by upregulation of p27, p57, PTEN, and PUMA (p53 upregulated modulator of apoptosis) [107]. In addition, CDF upregulated let-7 and miR-101 which suppressed the histone methyltransferase EZH2 associated with reduced survival, invasion and cancer stem cell function in pancreatic cancer [108]. The tumor suppressor miR-143 was likewise induced by CDF in pancreatic cancer cells as well as the tumor suppressor miR-146a leading to suppressed EGFR (epidermal growth factor receptor) signaling and inhibition of pancreatic tumor growth [109,110].

Another interesting synthetic curcuminoid is EF24 [3,5-bis(2-fluorobenzylidene)piperidin-4-one] which is easily prepared by condensation of piperidin-4-one with two equivalents of 2-fluorobenzaldehyde (Fig. 1) [111]. EF24 exhibited distinctly stronger growth inhibition and anti-angiogenic activity than curcumin [111,112]. Hence, it is not surprising that EF24 efficiently suppressed oncogenic miR-21 in prostate cancer (DU145) and melanoma (B16) cells and upregulated the miR-21 targets PTEN and PDCD4 [112]. A recent study of EF24 in melanoma cells disclosed significant effects on miR-33b expression, and suppression of EMT (=suppression of metastasis formation) as well as HMGA2 (high-mobility group AT-hook 2) inhibition were observed after treatment with EF24 associated with upregulation of miR-33b [113]. The miRNAs (both tumor suppressor and oncogenic ones) regulated by curcumin and its derivatives are presented in Table 2.

3.1.2. Garcinol

The phenolic natural product garcinol was isolated from the kokum tree (*Garcinia indica*) that grows in Western India [114]. Aside its application as a spice for Western Indian dishes, kokum is also applied in Ayurveda medicine for the treatment of infections and edema [115,116]. Chemically, garcinol (camboginol) is a type B polycyclic polyprenylated acylphloroglucinol (PPAP) featuring a benzophenone derivative with five isoprenyl side chains attached

to the phloroglucinol core (Fig. 1) [117]. Garcinol is easily isolated from dried kokum plums, however, there's a total synthetic procedure of garcinol and its close congener isogarcinol available now as well [118,119]. The chemical structure of garcinol shows some similarities with curcumin (β-diketone, phenol). Garcinol has revealed significant anticancer activity by targeting NF-κB, 5-lipoxygenase (5-LOX), and STAT proteins (for a recent review see ref. [118]). In addition, garcinol is a well-documented HAT inhibitor (histone acetylase inhibitor) and, thus, plays an important role for the epigenetic regulation of gene expression including the expression of oncogenes [120]. Synergistic effects were observed from combinations of garcinol with gemcitabine in pancreas cancer cells (including gemcitabine-resistant Panc-1 cells) due to garcinol-mediated modulation of miRNAs [121]. Garcinol downregulated oncogenic miR-21 (0.56-fold), miR-494 (0.97-fold), miR-495 (1.14-fold), and miR-1977 (0.80-fold) when compared with untreated pancreas cancer cells [121]. The expression of the micro-RNAs miR-453 (4.69-fold), miR-128 (1.82-fold), miR-1280 (0.46-fold) and miR-720 (0.43-fold) was upregulated by garcinol. The combination of garcinol with gemcitabine led to downregulation of miR-196a (0.82-fold), miR-495 (1.26-fold), miR-1914 (1.85-fold), miR-605 (2.42-fold), and miR-483-3p (1.06-fold) as well as upregulation of miR-638 (0.65-fold), miR-720 (0.41-fold), miR-453 (4.78-fold) and miR-663 (0.92-fold) [121]. Further to this, in breast cancer cells (MDA-MB-231, BT-549) garcinol reverted the metastasis-related EMT mechanism to the non-invasive MET (mesenchymal-to-epithelial transition) mechanism by induction of expression of the tumor suppressor miRNAs let-7a, let-7e, let-7f, miR-200b, and miR-200c both *in vitro* and *in vivo* in breast cancer xenograft models [122]. The microRNAs regulated by garcinol are presented in Table 2.

3.1.3. Flavanoids

The rich natural product class of the flavanoids (phenylchroman derivatives) comprises numerous bioactive compounds. In particular, soy isoflavones (3-phenylchromon derivatives) such as genistein (Fig. 2) and daidzein have shown promising anticancer effects including tumor growth inhibition and inhibition of metastasis formation by targeting multiple pathways (e.g., NF-κB, Akt, Wnt signaling, Notch signaling, androgen receptor signaling) [123]. Genistein downregulated the expression of oncogenic miR-21 in renal cancer cells (A498) followed by induction of p21 and p38 MAPK (mitogen-activated protein kinase) while cyclin E2 was suppressed by genistein [124]. In addition, numerous other oncogenic miRNAs are modulated by genistein. In renal cancer cells, downregulation of oncogenic miR-23b-3p was observed after treatment with genistein leading to expression of PTEN followed by suppression of PI3K (phosphatidylinositol-3-kinase), Akt and IL-32 (interleukin-32) [125]. Genistein reduced the levels of oncogenic miR-1260b in renal cancer cells (786-O, A498) and, thus, inhibited Wnt signaling via upregulation of the miR-1260b targets sFRP1 (frizzled-related protein 1), Dkk2 (dickkopf 2 homolog) and Smad4 (mothers against decapentaplegic 4) in these cancer cells [126].

Table 2
Regulation of non-coding RNAs/microRNAs by curcumin, curcumin derivatives (CDF, EF24), and garcinol.

| Compound	Tumor suppressors (up-regulated)	Oncogenes (down-regulated)
Curcumin	let-7, miR-7, miR-9, miR-15, miR-16, miR-22, miR-29a miR-145, miR-181b, miR-185, miR-192-5p, miR-200b/c, miR-203, miR-205-5p, miR-215, MEG3	miR-17-5p, miR-20a, miR-21, miR-27a, miR-186*, miR-208
CDF	miR-34, miR-101, miR-146a, miR-200, miR-874	miR-21, miR-210, miR-221
EF24	miR-33b	miR-21
Garcinol	let-7, miR-128, miR-200b/c, miR-453, miR-720, miR-1280	miR-21, miR-494, miR-495, miR-1977
Garcinol + Gemcitabine	miR-453, miR-663, miR-638, miR-720	miR-196a, miR-495, miR-605, miR-483-3p, miR-1914
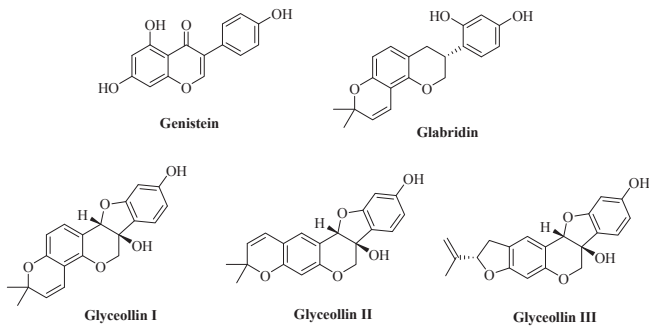
Fig. 2. Chemical structures of isoflavone derivatives.

Genistein performed analogously in prostate cancer cells (DU-145, PC-3) where suppression of miR-1260b and Wnt signaling was observed as well [127]. Oncogenic miR-27a was suppressed by genistein in various tumors including uveal melanoma (C918), pancreatic, and ovarian cancer (SKOV3) cells followed by induction of ZBTB10 (zinc-finger and BTB domain containing 10) and Sprouty2, the targets of miR-27a [128—130]. MiR-151, which targets various factors (e.g., N4BP1, CASZ1, SOX17, IL1RAPL1, ARHGDIA), features another miRNA suppressed by genistein in prostate cancer cells (PC-3, DU-145) leading to inhibition of migration and invasion of prostate cancer cells [131]. Further to this, genistein blocked miR-221 and miR-222 expression in prostate cancer cells (PC-3) followed by overexpression of ARH1 (aplysia ras homolog 1) and cell growth, invasion and colony formation inhibition [132]. MiR-223 was likewise suppressed by genistein in pancreatic cancer cells and induction of Fbw7 (F-box and WD-40 domain protein 7) expression was observed leading to cancer cell growth inhibition and apoptosis induction [133]. The G2535 mixture of isoflavones (70.54% genistein, 26.34% daidzein, 0.31% glycitein) reduced oncogenic miR-221 levels in pancreas cancer cells and inhibited proliferation and migration of pancreas cancer cells by induced expression of p27, p57, PTEN, and PUMA [107]. In highly metastatic breast cancer cells (MDA-MB-435), genistein suppressed miR-155 expression accompanied by increased expression of various pro-apoptotic and antiproliferative miR-155 targets (FOXO3, PTEN, casein kinase, p27) [134].

In contrast to that, the tumor suppressor miRNAs miR-34a, miR-574-3p and miR-1296 were upregulated in prostate cancer cells (PC-3, DU-145) after treatment with genistein [135—137]. While genistein-mediated induction of miR-34a knocked down HOTAIR (HOX transcript antisense RNA), overexpression of miR-574-3p suppressed anti-apoptotic Bcl-xL and enhanced caspase-3 and caspase-9 activity. Further targets of miR-574-3p included RAC1, EGFR and EP300 (p300 histone acetyl transferase), while miR-1296 blocks MCM2 (minichromosome maintenance) expression which is a crucial factor for functional DNA replication. However, a differing miRNA modulation by the isoflavones genistein and daidzein was observed in three prostate cancer cell lines [138]. Genistein also upregulated miR-34a in pancreas cancer cells and, thus, induced apoptosis and tumor cell growth inhibition by inhibition of Notch-1 signaling [139]. In addition, let-7 and miR-200 were upregulated in pancreatic cancer after treatment with genistein followed by suppression of miR-200 targets such as ZEB1 (zinc finger E-box-binding homeobox 1), slug and vimentin which are correlated with EMT [140]. Genistein also induced miR-146a expression associated with suppression of pancreatic cancer cell invasion via downregulation of miR-146a targets such as EGFR, MTA-2, IRAK-1, and NF-κB [141]. More recently, genistein exhibited distinct cell growth inhibition of breast cancer cells (MCF-7) by up-regulation of miR-23b expression (56.69-fold compared with untreated cells) [142].

Licorice (*Glycyrrhiza glabra*) is a well known sweetening plant and has been applied in folk medicine against inflammations, and as an antioxidant, antidote, demulcent and expectorant drug [143]. Extracts of licorice contain significant amounts of the isoflavan glabridin (a phytoestrogen, Fig. 2), which has shown anti-inflammatory, neuro- and cardioprotective activities in addition to distinct anticancer properties (growth inhibition, anti-angiogenic and anti-metastatic effects) [144—146]. Glabridin suppressed cancer stem cell-like features in hepatocellular carcinoma models (HepG2, Huh-7, MHCC97H) by upregulation of miR-148a and suppression of the miR-148a target SMAD2 (small body size mothers against decapentaplegic) associated with inhibition of TGF(transforming growth factor)-β/SMAD2 signaling [147]. Similar results were obtained from breast cancer cells (MDA-MB-231, Hs-578T) treated with glabridin [148]. In addition, glabridin inhibited angiogenesis of breast tumors (MDA-MB-231, Hs-578T) by upregulation of miR-520a [149]. The expression of NF-κB was blocked by upregulated miR-520a in glabridin-treated breast cancer cells associated with inhibition of NF-κB/IL-6/STAT-3 signaling.

Glyceollins represent further natural isoflavonoids biosynthetically derived from soy isoflavones (e.g., daidzein) which exhibited interesting anticancer properties (Fig. 2) [150]. These anti-estrogenic compounds efficiently stopped estrogen-induced tumor growth of breast and ovarian cancer models (MCF-7 by 53.4%, BG-1 by 73.1%) and suppressed estrogen-mediated expression of the progesterone receptor [151]. In letrozole-resistant breast cancer cells glyceollin I suppressed ZEB1 (zinc-finger E-box binding homeobox 1) expression leading to reversal of EMT in these resistant breast cancer cells [152]. In triple-negative breast cancer cells (MDA-MB-231, MDA-MB-468) a mixture of glyceollin I (68%), II (21%) and III (11%), isolated from soybean seeds incubated with *Aspergillus sojae*, reduced tumorigenesis by modulation of miRNAs. In particular, tumor suppressor miRNAs (miR181c, miR-181d) as well as EMT reversing miRNAs (miR-22, miR-29b, miR-29c, miR-30d, miR-34a, miR-195) were upregulated by glyceollins while oncogenic miRNAs increasing tumorigenesis (miR-21, miR-193a-5p), metastasis formation (miR-185, miR-224), migration and invasion (miR-486-5p) and mesenchymal cell maintenance (miR-542-5p) were downregulated by glyceollins [153]. The expression of NME1 (non-metastatic cells 1, target of miR-486-5p and miR-542-5p), was increased while vimentin (target of miR-30d) was reduced in glyceollins-treated breast cancer cells [153].

In addition to soy isoflavones, many natural flavanoid derivatives exhibited sound biological activities including antioxidant and anticancer properties. For instance, (-)-epigallocatechin-3-O-gallate (EGCG, Fig. 3), the main catechin flavanol of the tea plant (*Camilla sinensis*), revealed distinct anticancer activities by modulation of multiple targets [154]. The induction of apoptosis in hepatoma cells after treatment with EGCG was associated with an upregulation of the tumor suppressor miR-16 and inhibition of anti-apoptotic Bcl-2 [155]. In addition, miR-210 was induced by EGCG in lung cancer cells leading to cell growth inhibition [156]. However, the same group disclosed only modest changes of 21 miRNAs after EGCG treatment and that miR-210 played a minor role *in vivo*, while other miRNAs regulating Akt signaling, MAPK signaling and cell cycle control were of greater importance in lung cancer models *in vivo* [157]. For instance, down-regulation of miR-449c-5p (targets: ACSL1, elmod1, GAS1, ZFHX4), miR-374c-5p (targets: ART3, cnr1, DCN, EFNA5, GAS1, ELOVL6, rbm24), and miR-450a-2-3p (targets: cd19, IGFBP5, ZFHX4) as well as upregulation of miR-144-3p (targets: AMMECR3, Ccne2, ZCCHC2) and miR-34b-5p (targets: Ccne2, NRN1) was observed *in vivo* after EGCG treatment [157]. In melanoma cells, increased expression of let-7b via activation of 67LR (67-kDa laminin receptor) was observed after treatment with EGCG [158]. In addition, EGCG inhibited cell growth of osteosarcoma cells via upregulation of
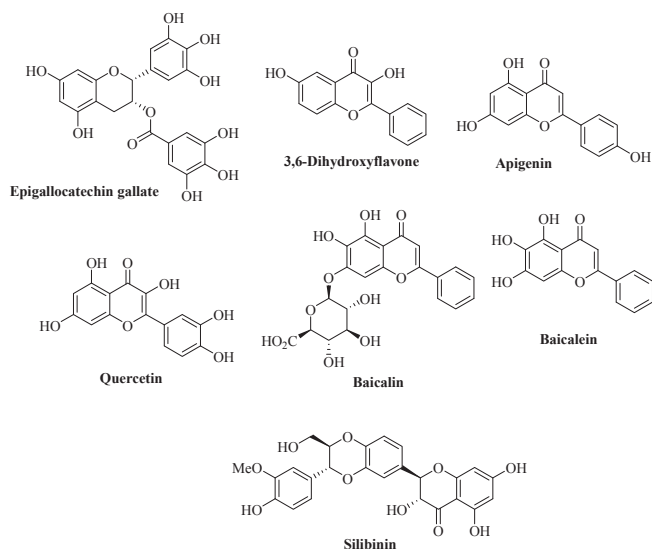
Fig. 3. Chemical structures of flavanoids.

miR-1 expression and induced apoptosis in osteosarcoma cells through induction of miR-126 expression [159,160]. Oncogenic miR-21 and AR (androgen receptor) signaling were suppressed in prostate cancer cells after EGCG treatment while miR-330 was upregulated leading to reduced prostate tumor growth [161]. The microRNAs miR-30* (which targets NF-κB, peroxisome-proliferator activated receptor/PPAR signaling, insulin signaling, glycolysis, gluconeogenesis, oxidative phosphorylation, glutathione, glycerolipids, and mitochondria), miR-453, miR-520-e, miR-608, and miR-629 were downregulated by EGCG in hepatoma cells (HepG2) [162]. Tsang and coworkers showed that 61 miRNAs were modulated by EGCG in hepatoma cells (HepG2) (e.g., upregulation of let-7c, miR-16, miR-18, miR-25, miR-92, and suppression of miR-129, miR-196, miR-200, miR-342, miR-526) [163]. EGCG-mediated suppression of miR-98-5p in NSCLC cells (A549) sensitized these tumor cells to cisplatin treatment [164]. The expression of further miRNAs was either reduced (oncogenic miR-92, miR-93, miR-106b) or increased (tumor suppressors miR-7-1, miR-34a, miR-99a) by a combination of EGCG with N-(4-hydroxyphenyl)retinamide in human neuroblastoma cells (SH-SY5Y, SK-N-DZ) [165]. Protection from UVB irradiation was observed in EGCG-treated dermal fibroblasts via modulation of various miRNAs [166]. Four miRNAs were upregulated (miR-1246, miR-548c-3p, miR-636, miR-933) and 14 miRNAs were downregulated (miR-1202, miR-1207-5p, miR-1225-5p, miR-1227, miR-1271, miR-133a, miR-134, miR-181d, miR-212, miR-362-3p, miR-455-5p, miR-494, miR-513a-5p, miR-660) in EGCG-treated dermal fibroblasts [166]. By the way, EGCG was shown to interact and to bind directly to certain miRNAs (miR-33a, miR-122) in liver cells and the miRNA binding ability of EGCG was determined by ^{1}H NMR spectroscopy [167].

The screening of a series of flavonoids revealed the outstanding activity of 3,6-dihydroxyflavone (3,6-DHF, Fig. 3) against breast cancer cells [168]. In addition, 3,6-DHF exhibited distinct chemopreventive effects in 1-methyl-1-nitrosourea treated breast cancer cells by upregulation of miR-34a and downregulation of miR-21 [169]. More recently, the same group disclosed an epigenetic mechanism for the modulation of miR-34a and miR-21 by 3,6-DHF in breast cancer cells [170]. Inhibition of the methyltransferase DNMT1 by 3,6-DHF (probably by binding to the cytosine pocket of the enzyme) blocked the hypermethylation of the miR-34a promoter which led to enhanced miR-34a expression [170]. Concerning miR-21, 3,6-DHF modulated histone modification and

depressed H3K9-14ac in the miR-21 promoter region which led to miR-21 suppression and efficient blocking of the PI3K/Akt/mTOR signaling pathway [170].

Apigenin represents another flavone derivative found in fruits, herbs, and vegetables, which induced apoptosis both via the intrinsic and via the extrinsic pathway and suppressed PI3K/Akt and ERK1/2 signaling pathways in various cancer cells (Fig. 3) [171,172]. Apigenin was shown to inhibit tumor growth both in vitro and in vivo [173,174]. Decreased expression of miR-138 enhanced the telomerase activity in tumor cells, which is associated with malignant growth [175]. The transfection with hTERT short hairpin RNA (a shRNA, which inhibits hTERT, human telomerase reverse transcriptase) in combination with apigenin treatment increased the expression of miR-138 in neuroblastoma cells [175]. In addition, miR-138 led to enhanced anticancer activity of apigenin and caused increased apoptosis induction and inhibition of tumor cell growth and colony formation of neuroblastomas (SK-N-DZ, SK-N-BE2) by apigenin both in vitro and in vivo [175]. Obesity and diabetes are considered as significant risk factors for various cancer diseases [176]. In particular, miR-103 overexpression is associated with glucose intolerance and apigenin efficiently lowered miR-103 levels by impairing the maturation of this miRNA and by inhibition of ERK-mediated TRBP (trans-activating response RNA-binding protein) phosphorylation [177]. In this way, the miR-103 suppressing properties of apigenin may contribute to the prevention of obesity- and diabetes-induced cancer types.

The consumption of a diet rich in the flavonol quercetin (Fig. 3), which is found in apples, grapes and onions, was associated with the modulation of various miRNAs in lung cancer tissues that play a distinct role for tumorigenesis including miR-146a (upregulation) and miRNAs of the let-7 and miR-26 family (tumor suppressing let-7 and miR-26 miRNAs were significantly expressed upon quercetin consumption) [178]. Quercetin-mediated miR-146a expression which inhibited NF-κB signaling was associated with anti-inflammation and cancer−preventive activity by protection of colonic myofibroblasts (CCD-18Co) from damage by ROS (reactive oxygen species) [179]. In addition, overexpression of let-7 by a combination of quercetin with catechins inhibited K-Ras signaling in pancreatic cancer cells as well as tumor growth inhibition [180]. In lung cancer cells (A549), quercetin induced miR-16 expression and decreased expression of the oncoprotein Claudin-2 in this way [181]. Unlike gemcitabine, quercetin also induced miR-142-3p expression in pancreatic cancer cells [182]. In hepatoma cells (HepG2), quercetin increased the levels of the tumor suppressor miR-34a associated with suppression of SIRT1 deacetylases in a p53-dependent way [183]. In contrast to that, oncogenic miR-27a was suppressed in colon cancer cells by quercetin in combination with resveratrol leading to enhanced apoptosis induction in the colon cancer cells [184]. However, quercetin reduced hepatic miR-125b-3p levels leading to enhanced GGH (γ-glutamyl hydrolase) expression which was linked to methotrexate resistance [185].

Baicalin and baicalein are flavones of the plant Scutellaria baicalensis Georgi (applied in TCM, Traditional Chinese Medicine) that exhibited distinct anti-inflammatory and anti-metastatic activities (Fig. 3) [186,187]. Baicalin induced expression of miR-23a and suppressed miR-378, miR-199a-3p and miR-181b in UVB-treated mice, all of them miRNAs that probably play a role for DNA repair mechanisms [188]. In addition, oncogenic miR-294 expression was reduced by baicalin in embryonic stem cells (ESCs) associated with suppression of the oncogenes c-jun and c-fos [189]. Baicalein exhibited anti-inflammatory activity by induction of miR-124 expression in neuronal cells (retinal ganglion cells) leading to suppression of the inflammation factor MCP-1 (monocyte chemotactic protein 1), an effect that might contribute to the chemopreventive properties of baicalein as well [190].

The flavolignan silibinin (Fig. 3) represents the active component of the fruits of the milk thistle (*Silybum marianum*) [191]. Recently, it was shown that silibinin suppressed miR-21 and enhanced miR-200c expression in erlotinib-resistant NSCLC tumors associated with a reversal of EMT and a suppression of mesenchymal markers (SNAIL, ZEB, N-cadherin) [192]. A list of microRNAs regulated by flavanoids is given in Table 3.

3.1.4. Stilbenes

The natural stilbene derivative resveratrol (3,4′,5-trihydroxystilbene) occurs in fruits such as grapes, berries, and plums and its anticancer properties against various cancer diseases were thoroughly investigated (Fig. 4) [193,194]. In colon cancer cells, resveratrol suppressed oncogenic miRNAs such as miR-17, miR-21, miR-25, miR-92a-2, miR-103-1, and miR-103-2, while tumor suppressor miR-663 (targeting TGF-β) was upregulated by resveratrol [195]. Oncogenic miR-21 was likewise downregulated by resveratrol in pancreatic cancer cells associated with enhanced apoptosis induction via suppression of the anti-apoptotic Bcl-2 protein [196]. Similar effects were observed from resveratrol-treated prostate cancer cells, where miR-21 suppression upregulated the miR-21 targets PDCD4 and maspin, and from gastric cancer cells treated with resveratrol [197,198]. The oncogenic miRNA clusters miR-17-92 and miR-106ab were suppressed by resveratrol in prostate cancer cells leading to PTEN induction [199]. Resveratrol-mediated downregulation of miR-520h blocked metastasis formation of lung cancer models by inhibition of FOXC2 (forkhead box C2) [200]. The combination of resveratrol and quercetin reduced miR-27a levels leading to ZBTB10 expression and apoptosis induction in HT-29 colon cancer cells [184]. Resveratrol inhibited proliferation of MCF-7 breast cancer cells by upregulation of miR-663 and miR-774 leading to EF1A2 (elongation factor 1A2) inhibition [201]. In addition, decreased cell invasion by induction of miR-141 and reversal of EMT via miR-200c upregulation (leading to ZEB1 suppression and E-cadherin upregulation) was observed after resveratrol treatment [202]. Synergy effects were observed in lung cancer cells from the combination of resveratrol with miR-200c [203]. Further to this, resveratrol-mediated up-regulation of the tumor suppressor miR-34a was associated with increased cell growth inhibition and apoptosis induction in colon cancer cells [204]. In addition, the tumor suppressor miR-34c was induced by resveratrol in colon cancer cells (HT-29, HCT-116) leading to increased apoptosis and suppression of the miR-34c target KITLG (also known as stem cell factor SCF) *in vitro* and *in vivo* [205]. The tumor suppressor miR-622 targets K-Ras and was found to be upregulated by resveratrol in transformed bronchial epithelial cells (16HBE-T) leading to cell cycle arrest and suppressed colony formation and tumorigenicity [206]. In hormone-sensitive breast tumors resveratrol inhibited DNA-methyltransferase DNMT3b by up-
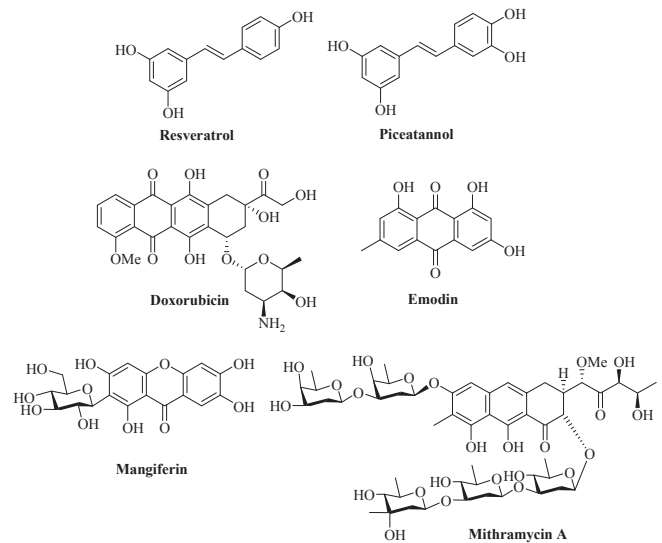

Fig. 4. Chemical structures of stilbenes, anthraquinones, xanthone and anthracene derivatives.

regulation of miR-129, miR-204, and miR-489 [207]. A general miRNA expression study in A549 lung cancer cells revealed that resveratrol suppressed miR-92a-2 and induced miR-299-5p, miR-194*, miR-338-3p, miR-758, and miR-582-3p which are likely involved in the regulation of proliferation, apoptosis, cell cycle and differentiation processes of lung cancer cells [208]. More recently, a similar study was carried out with triple-negative MDA-MB-231 breast cancer cells and resveratrol strongly upregulated miR-122-5p (37.6-fold) and significantly downregulated miR-542-3p (11-fold) and miR-200c-3p (8-fold) playing a key role for the anticancer effects of resveratrol in these cancer cells [209]. Like EGCG, resveratrol was able bind directly to certain miRNAs (miR-33a, miR-122) in liver cells and the miRNA binding ability of resveratrol was determined by ^{1}H NMR spectroscopy [167].

Piceatannol is a close stilbene analog of resveratrol (Fig. 4) and occurs in many fruits, in particular, in grapes and red wine which was associated with the so-called "French paradox" together with resveratrol. Indeed, piceatannol exhibited distinct anticancer properties via multiple pathways, and it revealed higher inhibition of COX-1/2 and CSN-associated kinase than resveratrol [210]. In leukemia cells (U937), Akt/Foxp3-mediated miR-183 expression was suppressed by piceatannol leading to inhibition of Sp1-induced metalloprotease ADAM17 expression and suppression of TNFα-induced NF-κB [211]. The expression of the tumor suppressor miR-129 was up-regulated by piceatannol in colon cancer cells

Table 3
Regulation of microRNAs by flavanoids.

Compound	Tumor suppressors (up-regulated)	Oncogenes (down-regulated)
Genistein	let-7, miR-23b, miR-34a, miR-146a, miR-200, miR-574-3p, miR-1296	miR-21, miR-23b, miR-27a, miR-151, miR-155, miR-221, miR-222, miR-223, miR-1260b
Glabridin	miR-148a, miR-520a	–
Glyceollins	miR-22, miR-29b, miR-29c, miR-30d, miR-34a, miR-181c, miR-181d, miR-195	miR-21, miR-185, miR-193a-5p, miR-224, miR-486-5p, miR-542-5p
EGCG	let-7b, let-7c, miR-1, miR-7-1, miR-16, miR-18, miR-25, miR-34a, miR-34b, miR-92, miR-99a, miR-126, miR-144-3p, miR-210, miR-330	miR-21, miR-30*, miR-92, miR-93, miR-98-5p, miR-106b, miR-374c-5p, miR-449c-5p, miR-450a-2-3p, miR-453, miR-520-e, miR-608, miR-629
3,6-DHF	miR-34a	miR-21
Apigenin	miR-183	miR-103 (glucose intolerance)
Quercetin	let-7, miR-16, miR-26, miR-34a, miR-146a, miR-142-3p	miR-27a, miR-125b-3p
Baicalin, Baicalein	miR-23a, miR-124 (anti-inflammatory)	miR-181b, miR-199a-3p, miR-294, miR-378
Silibinin	miR-200c	miR-21

(HCT-116, HT-29) and increased apoptosis was observed in piceatannol-treated cells via suppression of Bcl-2 (target of miR-129) [212]. Bone metastasis are difficult to tackle and cause painful and life-threatening bone damages, however, both resveratrol and piceatannol were shown to block osteoclastogenesis by downregulation of miR-183 via HO-1 (heme oxygenase-1) induction and, thus, feature suitable tools for the management and prevention of bone metastasis [213]. A list of miRNAs regulated by natural stilbenes is given in Table 4.

3.1.5. Anthraquinones, xanthone and anthracene derivatives

Doxorubicin (Adriamycin, Dox) is a natural anthracycline anticancer drug (inhibitor of topoisomerase II, isolated from *Streptomyces* bacteria) widely applied for the treatment of various advanced cancer diseases including metastatic breast cancer (Fig. 4) [214]. Resistance factors concerning doxorubicin treatment include the expression of ABC-transporters (increased drug efflux), enhanced drug metabolism, reduced topoisomerase II levels, altered p53 function, and apoptosis inhibition [214]. Restored miR-128 expression in breast cancer stem-like cells (bCSCs) enhanced the activity of doxorubicin and increased apoptosis and DNA damage in these drug resistant cells [215]. In addition, miR-451 regulated MDR1 (multidrug-resistance-protein 1) gene expression and played a crucial role for doxorubicin resistance in MCF-7 breast cancer cells [216]. Transfection of resistant breast cancer cells with miR-451 re-sensitized these cancer cells to doxorubicin treatment [216]. In addition, resistant MCF-7/DOX cells revealed downregulated let-7 (target: K-Ras), miR-27b (target: CYP1B1), miR-34a (target: Notch-1, E2F3), miR-127 (target: Bcl-6) and miR-200c (target: TCF8), while miR-21 (target: PTEN), miR-28 (target: BRCA1), miR-106a (target: RB1) and miR-206 (target: ERα) were upregulated in the doxorubicin-resistant MCF-7 cells [216]. Eroles and coworkers investigated the miRNA profile of doxorubicin-treated breast cancer cells and differences between MCF-7 cells and triple-negative breast cancer (TNBC) cells were observed (25 altered miRNAs were specific to TNBC cells, including miR-21-3p, miR-222-5p, miR-181a-3p, and miR-92a-1-5p) [217]. In addition, the miRNA miR-548c-3p mediated doxorubicin-resistance in resistant MCF-7 cells [217]. Further to this, receptor tyrosine kinase TrkB and repressor Bmi1 (B-cell-specific Moloney murine leukemia virus integration site 1) were identified as targets of miR-200c that mediate doxorubicin-resistance in breast cancer cells (BT474) upon down-regulation of miR-200c [218]. Doxorubicin-resistant MCF-7 breast cancer cells also exhibited reduced miR-125b and mir-193b expression associated with upregulated anti-apoptotic Mcl1 (myeloid cell leukemia 1) and inhibition of apoptosis [219,220]. In addition, drug-resistant breast cancer cells showed reduced miR-205 levels and restored miR-205 expression sensitized these breast cancer cells to TAC (docetaxol, doxorubicin, cyclophosphamide) treatment again via suppression of VEGFA and FGF2 and increased apoptosis induction [221]. Low levels of miR-218 were also observed in drug-resistant breast cancer cells, and re-expression of miR-218 broke the resistance to doxorubicin via inhibition of surviving [222]. MiR-450b-3p expression was significantly lowered in HER2/HER3-positive breast cancer cells as well as in patients with poor prognosis, while overexpression of miR-450b-3p directly inhibited HER3 expression leading to increased

sensitivity to doxorubicin [223]. Expression of oncogenic miR-181a upon genotoxic treatment induced doxorubicin-resistance in metastatic triple-negative breast cancers (TNBC) via STAT-3 activation and inhibition of pro-apoptotic Bax proteins [224]. Interestingly, the combination of a miR-10b-inhibitor (miR-10b is overexpressed in metastatic breast cancer) with low dose doxorubicin exhibited long-lasting remissions of metastatic breast cancer because of significant growth inhibition and apoptosis induction [225]. Another promising strategy to tackle TNBC was observed from targeted co-delivery of doxorubicin and miR-542-3p via hyaluronic acid-modified polyethyleneimine-poly(D,L-lactide-co-glycolide) (HA-PEI-PLGA) nanoparticles [226]. The restoration of miR-542-3p in TNBC cells treated with doxorubicin in this way enhanced apoptosis induction via p53 activation and survivin suppression [226]. The tumor suppressor miR-101 was downregulated in hepatocellular carcinoma (HCC) cells, and transfection of HCC cells with miR-101 sensitized these cells to treatment with doxorubicin via suppression of anti-apoptotic Mcl-1 [227]. Doxorubicin-resistant colon cancer cells (HT-29/Dox) exhibited low miR-522 levels and overexpression of miR-522 restored doxorubicin sensitivity via suppression of ABCB5 expression [228]. In addition, the mTOR-inhibitor sirolimus distinctly increased miR-34b expression in osteosarcoma cells leading to enhanced doxorubicin activity via suppressed PAK1 and ABCB1 expression [229]. In contrast to that, TGF-β1-mediated miR-202 expression blocked apoptosis induction in osteosarcoma cells and induced doxorubicin-resistance via downregulation of PDCD4 [230]. In glioblastoma cells (U87, LN229), the combination of doxorubicin with a miR-21 inhibitor (miR-21i) revealed increased anticancer effects by up-regulation of E-cadherin, RECK (reversion-inducing-cysteine-rich protein with kazal motifs), PTEN, VHL (Von Hippel-Lindau tumor suppressor), p21 and of tumor suppressor miRNAs (miR-200a/b, miR-429, miR-181d) while the tumor suppressor gene silencing DNA methyltransferase 1 (DNMT1) was suppressed by doxorubicin [231]. The application of a doxorubicin-conjugated miR-221 molecular beacon suppressed miR-221 expression efficiently while increased anticancer efficacy was observed in treated glioblastoma cells [232]. In diffuse large B-cell lymphoma (DLBCL) cells, the expression of miR-199a and miR-497 distinctly sensitized these lymphoma cells to doxorubicin treatment. In addition, better overall survival was observed in DLBCL patients with high miR-199a and miR-497 expression [233]. A list of miRNAs involved in doxorubicin-resistance is given in Table 5.

Emodin (1,3,8-trihydroxy-6-methylanthraquinone) features another natural anthraquinone derivative which was isolated from the roots of the Turkish rhubarb *Rheum palmatum*, a plant applied in TCM for the treatment of several diseases (Fig. 4) [234]. Emodin exhibited distinct anticancer activities via inhibition of tyrosine kinases [235]. Oncogenic miRNAs miR-221 and miR-222 were suppressed by emodin in leukemia cells (K562) leading to the induction of erythroid differentiation by upregulation of ALAS2 (aminolevulinate synthase) and of the tyrosine kinase c-KIT [235]. The growth inhibitory effects of emodin in lung cancer cells (A549) was associated with upregulation of miR-211 and miR-429 expression and suppression of their targets SATB2 (special AT-rich sequence-binding protein 2) and CRKL (Crk-like protein) [236]. The combination of emodin with curcumin revealed synergistic

Table 4
Regulation of microRNAs by stilbenes.

Compound	Tumor suppressors (up-regulated)	Oncogenes (down-regulated)
Resveratrol	miR-34a/c, miR-122-5p, miR-141, miR-194*, miR-200c, miR-299-5p, miR-338-3p, miR-582-3p, miR-622, miR-663, miR-758, miR-774	miR-17, miR-21, miR-25, miR-27a, miR-92a-2, miR-103-1, miR-103-2, miR-183, miR-200-3p, miR-520h, miR-542-3p, miR-17-92 cluster, miR-106ab cluster
Piceatannol	miR-129	miR-183

Table 5
MicroRNAs involved in doxorubicin-resistance of cancer cells.

Tumor suppressors (down-regulated)	Oncogenes (up-regulated)
let-7, miR-27b, miR-34a, miR-34b, miR-101, miR-125b, miR-127, miR-128, miR-193b, mir-199a, miR-200c, miR-205, miR-218, miR-450b-3p, miR-451, miR-497, miR-522, miR-542-3p	miR-10b, miR-21, miR-28, miR-106a, miR-181a, miR-202, miR-206, miR-221, miR-548c-3p

effects concerning the inhibition of breast cancer cell proliferation and invasion via upregulation of miR-34a and suppression of the miR-34 targets Bcl-2 and Bmi-1 [237]. In addition, emodin was able to suppress Wnt4/Dvl-1/β-catenin signaling by induction of miR-126 expression [238]. Angiogenesis of pancreatic cancer was blocked by emodin via upregulation of miR-20b and down-regulation of miR-155 and miR-210 leading to reduced TGF-β levels and inhibition of the TGF-β/Smad pathway [239].

Mangiferin represents an important bioactive component of the Mango plant (*Mangifera indica*) [240]. Chemically, mangiferin features a *C*-glucosidic xanthone (2-*C*-β-D-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone, Fig. 4) with potent antioxidant, anti-inflammatory, anti-diabetic, and anticancer activities (e.g., with activity against breast, colon, lung and prostate cancer as well as anti-leukemic activity) [240]. Inhibition of NF-κB and PPARγ was observed for mangiferin [240]. In prostate cancer cells (PC-3), mangiferin stopped cell growth and induced apoptosis via upregulated miR-182 expression associated with suppressed Bcl-2 expression [241]. In addition, apoptosis induction and levels of the tumor suppressor miR-15b were increased upon mangiferin treatment in glioma cells (U87) leading to reduced expression of MMP-9 which suggests an efficient inhibition of metastasis formation by mangiferin as well [242]. The anthracene derivative mithramycin A (aureoilic acid, plicamycin) was isolated from soil bacteria and revealed cell differentiation effects in myeloid leukemia [243]. In erythroleukemia cells (K562), mithramycin A induced leukemia cell differentiation by induction of miR-210 expression and γ-globin expression [244]. A list of microRNAs regulated by emodin, mangiferin and mithromycin A is shown in Table 6.

3.1.6. Miscellaneous phenols

Ellagitannins represent natural galloyl and caffeoyl esters of glucose isolated from the parasitic plant *Balanophora japonica* that grows on symploco plants in southern China and Japan and which is applied as antidote and hemostatic agent in TCM (Traditional Chinese Medicine) [245]. Derivative BJA3121 (1,3-di-*O*-galloyl-4,6-hexahydroxydiphenoyl-β-D-glucopyranose) revealed growth inhibitory effects on hepatoma cells (HepG2) and modulated the expression of various miRNAs (e.g., upregulation of let-7e), however, tumor suppressors were also downregulated (let-7a) and oncomiRs were upregulated (miR-373*) by BJA3121 in these cells [246]. In contrast to that, HepG2 hepatoma cells treated with its close analog BJA32515 (1,3,4-tri-O-galloyl-6-O-caffeoyl-β-D-glucopyranose) exhibited increased expression of the tumor suppressors let-7a and miR-29a while oncogenic miR-373 and miR-197 were suppressed (Fig. 5) [247]. Pomegranate (*Punica granatum* L.) is rich in polyphenolic compounds and pomegranate extracts exhibited

distinct anticancer and anti-inflammatory activities. These properties correlated with the inhibition of NF-κB and further inflammatory factors in various cancer cells [248]. A pomegranate extract with significant contents of the ellagitannins punicalagin A, punicalagin B (Fig. 5), and of the anthocyanins delphinidin-3-glucoside and cyanidin-3-glucoside was tested against breast cancer cells (BT-474, MDA-MB-231) [248]. Indeed, the pomegranate extract reduced miR-27a levels in these breast cancer cells associated with increased ZBTB10 (=Sp-repressor) expression and reduced levels of Sp, VEGF, VEGFR (vascular endothelial growth factor receptor) and survivin [248]. In addition, pomegranate extract suppressed miR-155 leading to upregulation of inositol phosphatase SHIP-1 and inhibition of PI3K/Akt signaling [248]. Pomegranate extract also suppressed DNA repair and led to double-strand breaks (DSBs) accompanied by increased apoptosis in MCF-7 breast cancer cells via upregulation of miR-24 and miR-183 [249]. Pomegranate extracts likewise induced miR-34a expression depending on activated p53 leading to suppression of c-Myc and CD44 and increased apoptosis induction in EJ bladder cancer cells [250].

1′-Acetoxychavicol acetate (Fig. 5), a phenolic compound isolated from *Alpinia conchigera* (wild ginger), modulated the expression of miRNAs in cervix carcinoma cells (Ca Ski, HeLa) [251]. More precisely, the tumor suppressor miRNAs miR-138, miR-210 and miR-744 were upregulated by 1′-acetoxychavicol acetate in combination with cisplatin [251]. In addition, oncogenic miR-23a was suppressed in head-and-neck squamous cells (HN4) associated with PTEN upregulation and increased apoptosis induction after treatment with 1′-acetoxychavicol acetate [252].

Table 6
Regulation of microRNAs by emodin, mangiferin, and mithramycin A.

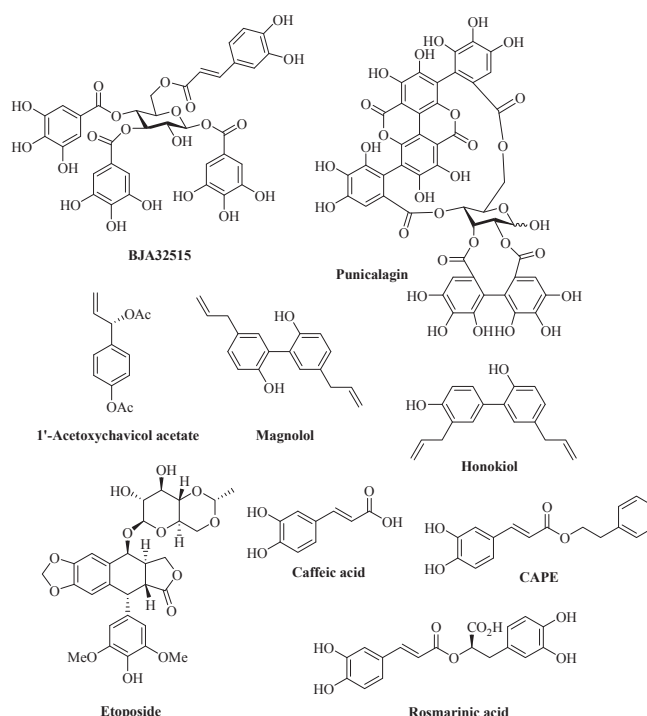| Compound	Tumor suppressors (up-regulated)	Oncogenes (down-regulated)
Emodin	miR-20b, miR-34a, miR-126, miR-211, miR-429	miR-155, miR-210, miR-221, miR-222
Mangiferin	miR-15b, miR-182	–
Mithramycin A	miR-210	–

Fig. 5. Miscellaneous phenolic derivatives.

The biphenol magnolol, [4-allyl-2-(5-allyl-2-hydroxyphenyl) phenol], was isolated from *Magnolia obovata* which has been applied in the Japanese folk medicine for the treatment of cough and gastrointestinal diseases (Fig. 5) [253]. Magnolol exhibited growth inhibitory and anti-metastatic activity against various cancer types and suppressed Wnt signaling in colon cancer cells [253]. In breast cancer cells (MCF-7), the expression of the tumor suppressor miR-200c was increased after treatment with magnolol leading to ZEB1 inhibition and E-cadherin upregulation [254]. Honokiol, [2-(4-hydroxy-3-prop-2-enyl-phenyl)-4-prop-2-enyl-phenol], features a close analog of magnolol which was isolated from various *Magnolia* species (*M. officinalis*, *M. obovata*, *M. grandiflora*) of Southeast and East Asia (Fig. 5) [255]. The biphenol honokiol revealed distinct anti-oxidative, anti-inflammatory and anticancer activities by targeting multiple factors including signaling pathways of NF-κB, EGFR, STAT-3 and mTOR (mammalian target of rapamycin) [256]. In breast tumors, honokiol inhibited tumor growth via increased expression of miR-34a and STAT-3 inhibition associated with suppression of the Wnt1-MTA-β-catenin signaling pathway [257]. Honokiol also inhibited the growth of bladder tumors by increased expression of the tumor suppressor miR-143 leading to suppression of EZH2, MMP-9, CD44, and Sox2 [258].

Caffeic acid (3,4-dihydroxycinnamic acid) and its phenethyl ester CAPE belong to the active constituents of the propolis extract, a honey bee hive extract, and also occur in various plants (Fig. 5) [259]. Caffeic acid and CAPE exhibited distinct antioxidant, anti-inflammatory and anticancer properties [260,261]. A significant suppression of angiogenesis was observed after treatment with caffeic acid and CAPE [259]. In hepatocarcinoma cells (HepG2, MHCC97H), caffeic acid increased miR-124 levels via DNA-demethylation associated with suppression of NF-κB/p65, STAT-3, and IL-6 (interleukin-6) [262]. In addition, caffeic acid suppressed cancer stem cell-like features by induction of miR-148a leading to inhibition of the TGF-β/SMAD2 signaling pathway and blocking of SMAD2 expression by miR-148a that binds to the *SMAD2*-3′UTR [263]. CAPE downregulated pro-inflammatory miRNAs (miR-9, miR-125b, miR-146a, and miR-155) in neuronal cells exposed to Alzheimer's disease derived extracellular fluid via inhibition of NF-κB which might play a role for the anticancer properties of CAPE as well [264]. Rosmarinic acid (isolated from rosemary, *Rosmarinus officinalis*) features another caffeate derivative with distinct antioxidant, anti-inflammatory and anticancer effects (Fig. 5) [265]. In gastric cancer cells (MKN45), rosmarinic acid revealed an anti-Warburg effect, i.e., it suppressed glycolytic biosynthesis of ATP which is a common feature of many cancer types [266]. Down-regulation of the microRNAs miR-155, miR-146a and miR-223 was observed after treatment with rosmarinic acid as well as suppression of STAT-3, IL-6 and HIF-Iα (hypoxia inducible factor) [266]. Table 7 provides a list of miRNAs modulated by various phenolic natural compounds.

Table 7
Regulation of microRNAs by miscellaneous phenols.

Compound	Tumor suppressors (up-regulated)	Oncogenes (down-regulated)
BJA32515	let-7a, miR-29a	miR-197, miR-373
Pomegranate extract	miR-24, miR-183	miR-27a, miR-155
1′-Acetoxychavicol acetate	miR-138, miR-210, miR-744	miR-23a
Magnolol	miR-200c	–
Honokiol	miR-34a, miR-143	–
Caffeic acid, CAPE, Rosmarinic acid	miR-124, miR-148a	miR-9, miR-125b, miR-146a, miR-155, miR-223

The topoisomerase II inhibitor and approved anticancer agent etoposide is derived from the natural product podophyllotoxin and is applied in advanced stages of breast cancer, lung cancer, leukemia and lymphoma diseases (Fig. 5) [267,268]. Dean and coworkers investigated the influence of miRNAs on etoposide sensitivity and etoposide resistance of breast cancer cells (sensitive MCF-7, resistant MCF-7/VP) [269]. A significant upregulation of miR-382, miR-23b and miR-885-5p (>2-fold) and suppression of miR-218, miR-758 and miR-548d-5p (>2-fold) was observed from etoposide-resistant MCF-7/VP cells when compared with sensitive MCF-7 cells [269]. MiR-218 was particularly down-regulated (7.79-fold) in the resistant MCF-7/VP cells. The authors assumed a link between the modulation of these miRNAs with the significant upregulation of ABC transporters such as ABCC1 and ABCC6 in the resistant MCF-7/VP cells, which remove etoposide from the cancer cells again [269]. Recently, increased levels of miR-124 upregulated the CDK (cyclin-dependent kinase) inhibitor p27 leading to G1 arrest and sensitized breast and ovarian cancer tumors to etoposide treatment [270]. In hepatoma carcinoma, increased miR-23a expression enhanced the activity of etoposide by suppression of topoisomerase 1, the target of miR-23a, and miR-23a expression depended on functional p53 [271]. HepG2 hepatoma cells were turned into etoposide-resistant cells by upregulation of miR-210 (induced by hypoxia) while upregulation of miR-196b sensitized hepatoma cells to etoposide via suppression of IGF2BP1 (insulin-like growth factor 2 RNA binding protein 1) [272]. Expression of miR-1915-3p in lung cancer cells inhibited etoposide-induced apoptosis by suppression of DRG2 (developmentally regulated GTP-binding protein 2) and PBX2 (pre-B cell leukemia homeobox 2) [273]. In contrast to that, expression of miR-1469 enhanced apoptosis induction by etoposide in lung cancer cells via suppression of STAT5A [274]. The induction of miR-153 reduced the anticancer activity of etoposide in HCC cells via upregulation of survivin and Bcl-2, and inhibition of p21, PTEN and FOXO1 [275]. In addition, osteosarcoma cells responded to etoposide treatment by activation of the tumor suppressor miR-34a in a p53-dependent way [276]. A list of miRNAs involved in etoposide-resistance and −sensitivity is provided in Table 8.

3.2. Terpenoids

3.2.1. Triterpenes

Boswellic acids (Fig. 6) represent the major triterpene constituents of the resin of the plant *Boswellia serrata* and were found to be potent anti-inflammatory agents (5-LOX inhibitors) [277]. In addition, significant anticancer properties were observed for boswellic acids including the complete remission of brain metastases in a breast cancer patient after consumption of commercially available *Boswellia* extract [278]. The most active boswellic acid is AKBA (3-acetyl-11-keto-β-boswellic acid) which induced apoptosis and blocked invasion of cancer cells by inhibition of NF-κB and STAT-3 signaling [279,280]. In colon cancer models, AKBA enhanced the expression of the tumor suppressors let-7 and miR-200 both *in vitro* and *in vivo* leading to reduced CDK6 (cyclin-dependent kinase 6) and vimentin levels [281]. In combination with curcumin, AKBA upregulated the tumor suppressor miR-34a in colon cancer

Table 8
MiRNAs involved in etoposide resistance and sensitivity.

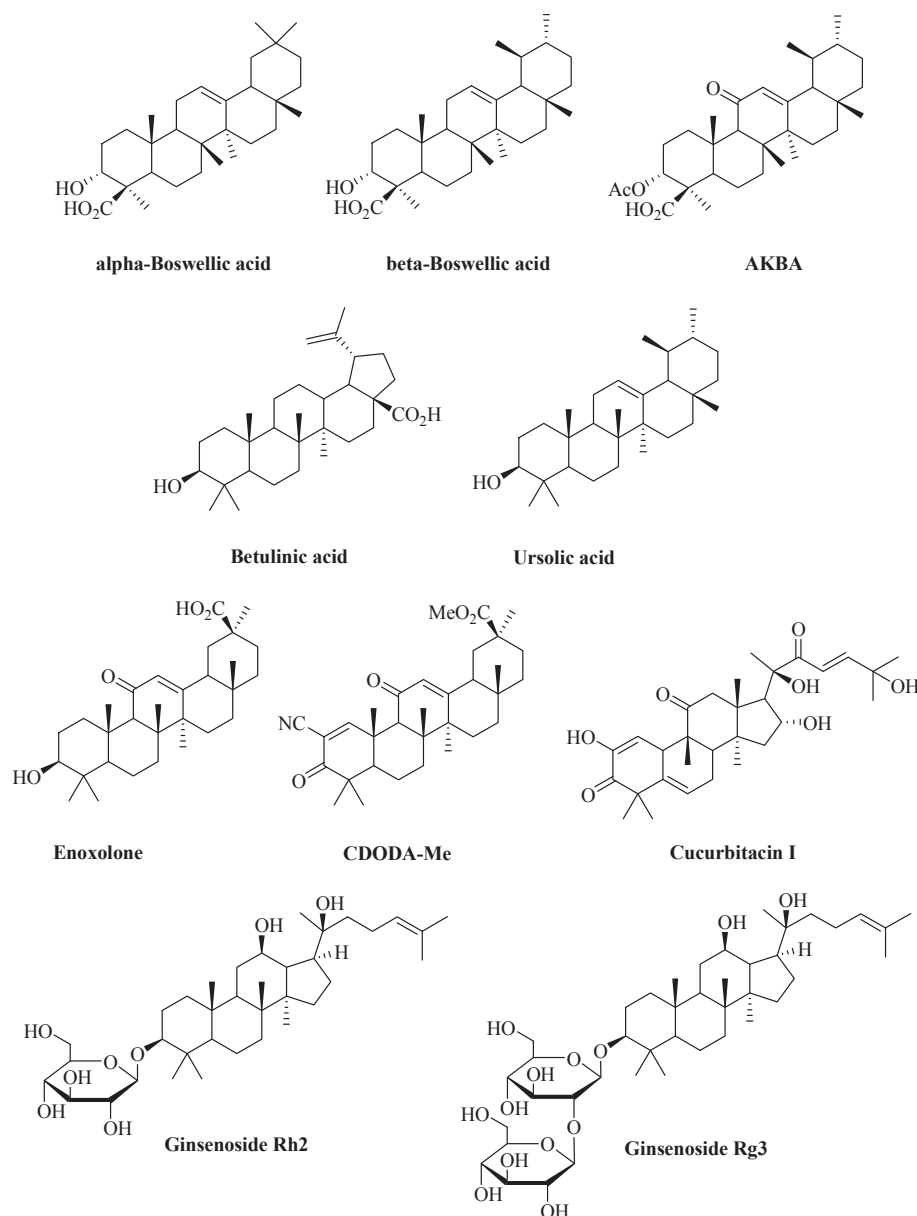| Etoposide-resistance	Etoposide-sensitivity
miR-23b, miR-153, miR-210, miR-382, miR-885-5p, miR-1915-3p	miR-23a, miR-34a, miR-124, miR-196b, miR-218, miR-548d-5p, miR-758, miR-1469

Fig. 6. Chemical structures of triterpene derivatives.

cells, while miR-27a was suppressed by AKBA and curcumin. The modulation of these miRNAs was also observed from colon cancer xenografts (HCT-116) upon treatment with AKBA and curcumin associated with tumor growth inhibition when compared with untreated tumors [282].

The bioactive triterpene betulinic acid (Fig. 6) occurs in birch and plane trees and is easily isolated in significant amounts from the fallen bark of plane trees (*Platanus acerifolia*) [283]. Betulinic acid has revealed topoisomerase I inhibition and exhibited distinct and selective anticancer activity in mouse xenografts (ovarian cancer, melanoma) while it was non-toxic to the organism at doses up to 500 mg/kg [284,285]. In colon cancer cells (RKO, SW480), betulinic acid exhibited growth inhibitory and pro-apoptotic effects via suppression of miR-27a and induction of the Sp repressor ZBTB10 (miR-27a target) [286]. Similar effects were observed from estrogen-negative breast cancer cells (MDA-MB-231) after treatment with betulinic acid [287]. Interestingly, the usually oncogenic miR-21 was upregulated by betulinic acid in hepatoma cells in a

p53-dependent way and contributed to the pro-apoptotic properties of betulinic acid by suppression of Sod2 [288]. In this special case, miR-21 revealed clear tumor suppressor properties upon activation by betulinic acid. In addition, betulinic acid suppressed miR-33 and NF-κB in lipopolysaccharide-treated macrophages and promoted the expression of the ABC-transporter ABCA1 that is responsible for the transport of cholesterol and phospholipids [289].

Ursolic acid features another natural triterpene found in herbal drug plants such as *Radix actinidiae* and *Oldenlandia diffusa* and revealed significant anti-inflammatory and anti-cancer activities (Fig. 6) [290,291]. In U251 glioma cells, ursolic acid inhibited tumor cell growth via reduced miR-21 expression associated with increased expression of apoptotic PDCD4 and caspase-3 activation as well as blocked TGF-β/SMAD signaling [292].

Aside glabridin isoflavans, licorice extracts also contain significant amounts of the triterpene glycyrrhetinic acid (enoxolone, up to

24% in licorice root extracts) which showed strong apoptosis induction in cancer cells (Fig. 6) [293]. Enoxolone blocked tumor cell invasion via upregulated miR-200c expression in breast cancer cells accompanied by ZEB1 suppression and E-cadherin upregulation [254]. The semi-synthetic glycyrrhetinic acid derivative CDODA-Me (methyl 2-cyano-3,11-dioxo-18β-olean-1,12-dien-30-oate, Fig. 6) inhibited colon cancer growth (RKO, SW480) *in vitro* and *in vivo* via reduction of miR-27a levels associated with increased expression of the Sp repressor ZBTB10 and upregulation of Myt-1 which causes G2/M arrest by cdc2 phosphorylation [294]. Interestingly, the gap junction blocker 18α-glycyrrhetinic acid (18-AGA) was able to inhibit the intercellular transfer of miRNAs efficiently [295].

Cucurbitacins represent further triterpenes with amazing biological properties. Cucurbitacin I (Fig. 6), for instance, inhibited JAK/STAT-3 signaling accompanied with strong anticancer activity in mice [296]. CD4+ T cells (cutaneous T-cell lymphoma, Sézary syndrome) treated with cucurbitacin I showed reduced IL-21-mediated oncogenic miR-21 expression and, thus, IL-21 promoted miR-21 expression strongly depended on STAT-3 activation [297]. Apoptosis induction in CD4+ T cells by cucurbitacin I was in parts mediated by miR-21 suppression. Similarly, the IL-21-induced and STAT-3 dependent expression of miR-155 was downregulated by cucurbitacin I [298]. In addition, STAT-3 targeting/suppressing miRNAs such as miR-337-3p revealed synergistic effects in combination with cucurbitacin I in NCI-H1155 lung cancer cells and the IC$_{50}$ values of cucurbitacin I were improved in these cells when co-treated with miR-337-3p (IC$_{50}$ = 0.37 μM in miR-337-3p co-treated cells, IC$_{50}$ = 1.14 μM for cucurbitacin I alone) [299].

Ginsenosides are triterpene saponins with a terpenoid steroidal nucleus connected to a sugar fragment and were isolated from the ginseng plant that is widely applied as a herbal drug both in East Asia and in the West [300]. In glioma cells (U251), ginsenoside Rh2 (Fig. 6) induced miR-128 expression and suppressed miR-21 associated with tumor cell growth inhibition and apoptosis induction in these tumor cells [301]. The Rh2-mediated modulation of microRNA expression of A549 non-small cell lung cancer cells was determined and miR-148a was distinctly upregulated (9.59-fold) by Rh2 in these lung cancer cells [302]. MiR-148a expression revealed significant antitumor effects in various cancer models and, thus, likely contributes to the anticancer effects of Rh2 as well. In addition, oncogenic miR-21, miR-23b, miR-27b, miR-100, miR-221 (4-9-fold) and miR-424 (12.4-fold) were downregulated by Rh2 in A549 lung cancer cells [302]. Ginsenoside Rg3 features another triterpene saponin derivative of red ginseng that efficiently blocked angiogenesis via upregulation of miR-520h leading to suppression of the ephrin receptors EphB2 and EphB3 (Fig. 6) [303]. A list of microRNAs regulated by triterpenes is presented in Table 9.

3.2.2. Diterpenes, sesquiterpenes and monoterpenes

Paclitaxel (taxol) is a clinically approved natural diterpene anticancer drug initially isolated from the Pacific yew (*Taxus brevifolia*) that induces cell death via microtubule stabilization (Fig. 7) [304,305]. The formation of paclitaxel resistance is a serious
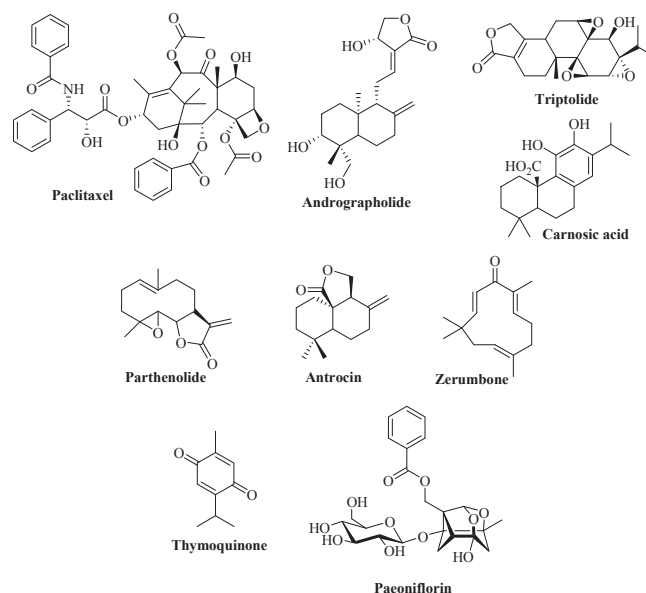

Fig. 7. Chemical structures of di-, sesqui- and monoterpenes.

problem in the clinics and miRNAs are involved in sensitivity or resistance to paclitaxel. Forty human cancer cell lines were investigated for miRNAs involved in *in vitro* sensitivity to paclitaxel and two miRNAs, miR-30a-5p and miR-367, were identified to play a crucial role [306]. While expression of miR-367 increased paclitaxel activity, expression of miR-30a-5p reduced paclitaxel efficacy in cancer cells [306]. In ovarian cancer cells (A2780), paclitaxel sensitivity was associated with miR-149 downregulation and enhanced MyD88 expression [307]. In addition, increased expression of miR-320a, miR-22 and miR-129-5p as well as reduced expression of miR-9, miR-155 and miR-640 were observed in ovarian cancer cells resistant to paclitaxel (ST30 cells) [308]. The miR-9 target RAB34 (a GTPase) might play a role for the observed paclitaxel-resistance [308]. MiR-433 features another oncogenic miRNA that is upregulated in paclitaxel-resistant ovarian cancer cells (A2780) leading to suppression of CDK6 and to cellular senescence [309]. In addition, expression of miR-130b and of miR-197 contributed to paclitaxel-resistance in ovarian cancer cells [310,311]. Paclitaxel-resistant epithelial ovarian cancer revealed high levels of miR-1307, which was associated with drug resistance [312]. Mimics of miR-200c and miR-141 sensitized drug-resistant ovarian carcinoma cells (MES-OV) to paclitaxel treatment via reversal of EMT (induction of E-cadherin, suppression of vimentin) [313]. Further to this, expression of miR-873 downregulated the drug efflux transporter ABCB1 and increased the anticancer activity of paclitaxel in ovarian cancer cells [314]. Distinctly increased expression of miR-622 and miR-663 featured bad prognosis factors for patients suffering from taxol-resistant ovarian cancer, while expression of miR-647 indicated good prognosis for taxol-sensitive ovarian cancer patients [315]. The expression of miR-125a

Table 9
Interaction with and regulation of microRNAs by triterpenes.

Compound	Tumor suppressors (up-regulated)	Oncogenes (down-regulated)
Boswellic acids (AKBA)	let-7, miR-34a, miR-200	miR-27a
Betulinic acid	miR-21(!)	miR-27a, miR-33
Ursolic acid	–	miR-21
Glycyrrhetinic acid derivatives	miR-200c	miR-27a
Cucurbitacin I	(synergism with miR-337-3p)	miR-21, miR-155
Ginsenosides (Rh2, Rg3)	miR-148a, miR-520h	miR-21, miR-23b, miR-27b, miR-100, miR-221, miR-424

Table 10
MiRNAs involved in paclitaxel resistance and sensitivity.

Paclitaxel-resistance	Paclitaxel-sensitivity
miR-19a, miR-21, miR-22, miR-30a-5p, miR-129-5p, miR-130b, miR-149, miR-153, miR-133a/b, miR-197, miR-205, miR-320a, miR-361-3p, miR-375, miR-433, miR-490, miR-520h, miR-622, miR-663, miR-1307	let-7b, miR-9, miR-10b, miR-16, miR-17, miR-17-5p, miR-34a, miR-122, miR-125a, miR-130a, miR-134, miR-141, miR-155, miR-200c, miR-218, miR-367, miR-494, miR-497, miR-647, miR-873, miR-877, miR-1204

sensitized cervical cancer to paclitaxel treatment via suppression of STAT3, while miR-375 expression reduced paclitaxel sensitivity by induction of EMT processes [316,317]. MiR-490-3p features another oncomir in ovarian cancer cells that mediates paclitaxel resistance via upregulation of Pgp and GST-π [318]. Induction of miR-134 in endometrial cancer cells (ECS) promoted paclitaxel activity by inhibition of POGLUT1 (protein O-glucosyltransferase 1) and Notch signaling [319]. Reduced levels of miR-218 were found in taxol-resistant breast cancer cells, and re-expression of miR-218 broke the resistance to taxol via inhibition of survivin [222]. Upregulation of the RNA-processing enzyme Dicer induced the expression of miR-494 and increased the activity of paclitaxel in breast cancer via suppression of AXL kinase [320]. In contrast to that, expression of miR-520h promoted paclitaxel-resistance in breast cancer cells associated with inhibition of DAPK2 (death-associated protein kinase 2) expression [321]. Breast cancer cells expressing miR-621 inhibited FBXO11 expression and activated p53 leading to enhanced sensitivity to paclitaxel treatment [322]. Patients suffering from luminal A subtype breast cancer resistant to neo-adjuvant chemotherapy (NAC, paclitaxel plus epirubicin) exhibited distinctly stronger expression of miR-19a and miR-205 than drug-sensitive patients [323]. In addition, breast cancer patients who received NAC exhibited increased expression of miR-34a and miR-122, which may contribute to the anticancer activity of paclitaxel and epirubicn [324]. In paclitaxel-resistant lung cancer cells, miR-16 and miR-17 were downregulated leading to induction of anti-apoptotic Bcl-2, and expression of miR-16 and miR-17 enhanced apoptosis induction by paclitaxel via suppression of Bcl-2 as well as autophagy inhibition via Beclin-1 downregulation [325]. In addition, miR-17-5p was downregulated in paclitaxel-resistant lung cancer cells accompanied by Beclin-1 upregulation [326]. A pH-dependent liposomal formulation of a combination of antagomir-10b and paclitaxel released antagomir-10b and paclitaxel at lower pH values and inhibited lung metastasis formation and tumor growth inhibition of 4T1 breast tumors by suppression of miR-10b [327]. Another formulation of a special copolymer including polyethylene glycol 5000, vitamin E and diethylenetriamine (PEG$_{5K}$-VE$_4$-DET$_{20}$) was loaded with a let-7b mimic and paclitaxel and exhibited increased anticancer activity (increased growth inhibition and apoptosis induction as well as reduced invasiveness) in KRAS-mutant lung cancer (A549) both in vitro and in vivo [328]. In gastric cancer cells (SGC7901), miR-21 expression mediated paclitaxel-resistance and inhibition of miR-21 restored paclitaxel activity in these cancer cells via suppression of the drug efflux transporter P-gp [329]. Patients suffering from metastatic and recurrent gastric cancer with low levels of miR-1 and miR-27a revealed better responses to a combination of paclitaxel and fluoropyrimidine than patients with high expression of miR-1 and miR-27a [330]. Downregulation of miR-203 was observed in paclitaxel-resistant colon cancer cells, and induced expression of miR-203 suppressed SIK2 (salt-inducible kinase 2) expression leading to sensitization to paclitaxel [331]. In HCT-116 colon cancer cells, upregulation of miR-497 suppressed the oncogene Smurf1 leading to increased paclitaxel activity [332]. In paclitaxel-resistant prostate cancer cells, miR-130a was downregulated and re-expression of miR-130a promoted the activity of paclitaxel via apoptosis activation [333]. Paclitaxel-resistant nasopharyngeal carcinoma (NPC)

cells (CNE-1/Taxol) showed low expression both of miR-634 and of miR-1204, and restored miR-634 and miR-1204 expression sensitized NPC cells to paclitaxel treatment in vitro and in vivo again [334,335]. The expression of miR-153 diminished the anticancer activity of paclitaxel in HCC cells via upregulation of survivin and Bcl-2, and inhibition of p21, PTEN and FOXO1 [275]. In addition, treatment of HCC cells with paclitaxel upregulated the tumor suppressor miR-877 and induced tumor cell growth inhibition by suppression of FOXM1 [336]. Inhibition of miR-133a/b and miR-361-3p induced cell cycle arrest (S phase arrest) and apoptosis (activation of caspase-3/7) and enhanced distinctly the anti-proliferative effects of paclitaxel in NSCLC cells (H1993) [337]. A list of miRNAs involved in paclitaxel-resistance and –sensitivity is provided in Table 10.

The labdane diterpene andrographolide of *Andrographis paniculata* has revealed chemopreventive effects and protected A549 alveolar epithelial cells from damages induced by cigarette smoke (Fig. 7) [338]. In these cells, andrographolide increased the expression of miR-218 accompanied by reduced NF-κB signaling (reduced IκB-α phosphorylation and lowered p65 accumulation in the nucleus) leading to reduced inflammation [338]. In addition, andrographolide increased the expression of miR-23a-5p, miR-30b-5p, miR-106b-5p and miR-222-3p in hepatoma cells leading to hepatoma growth inhibition [339].

Triptolide features an anticancer active diterpene triepoxide lactone of the Chinese plant *Tripterygium wilfordii* (thunder god vine, applied in TCM) and suppressed the heat shock protein Hsp70 in cancer cells associated with cancer cell growth inhibition (Fig. 7) [182]. Unlike the approved anti-pancreatic cancer drug gemcitabine, triptolide also induced miR-142-3p expression (a miRNA repressor of Hsp70) in pancreatic cancer cells, while minnelide, the water-soluble triptolide prodrug, increased miR-142-3p expression in vivo in a pancreatic cancer xenograft model [182]. Further to this, triptolide augmented the MDM2-suppressing effects of miR-339-5p both in MCF-7 breast cancer and in HCT-116 colon cancer cell lines after induction of the p53 inhibitor MDM2 by the approved anticancer drug 5-FU [340].

Aside rosmarinic acid, rosemary (*Rosmarinus officinalis* L.) extracts also contain bioactive diterpenes such as carnosol and carnosic acid (Fig. 7) [341]. Both carnosol and carnosic acid showed antitumor activity against pancreatic and colon cancer both in vitro and in vivo by suppression of miR-15b and induction of glycosyltransferase GCNT3 [342]. In addition, carnosic acid in combination with 1,25-dihydroxyvitamin D$_3$ reduced miR-181a levels in leukemia cells (HL-60, U937) leading to cell cycle arrest and cell differentiation [343].

Sesquiterpenes have shown potent anticancer activities, for instance, the fungal compound class of illudins exhibited strong tumor growth inhibitory activity via unique DNA binding properties [344]. The sesquiterpene lactone parthenolide (Fig. 7) isolated from feverfew (*Tanacetum parthenium*) has also shown distinct anticancer activity in various cancer cell lines and parthenolide showed NF-κB inhibition and DNA hypomethylation via DNMT1 suppression [345]. Thus, miRNA modulation by parthenolide was assumed and in acute myelogenous leukemia cells (MOLM-13), parthenolide indeed increased the expression of the known tumor suppressors miR-15a and miR-16 [346].

The medicinal fungus *Antrodia camphorata* contains the sesquiterpene lactone antrocin (Fig. 7) that has revealed strong anticancer activity in triple-negative breast cancer cells (MDA-MB-231) [347]. In addition, antrocin revealed growth inhibition and apoptosis induction in lung cancer cells (H441, gefitinib-resistant H1975) via increased let-7c expression associated with STAT3 inhibition [348]. Another Southeast Asian ginger sesquiterpene, zerumbone (Fig. 7), induced apoptosis in Panc-1 pancreatic cancer cells via increased expression of miR-34 accompanied by p53 and p21 activation [349].

Monoterpenes such as menthol have shown antitumor activity against various cancer cells, and monoterpene conjugates even overcame cisplatin-resistance [350–352]. Thymoquinone (TQ, Fig. 7) represents the active monoterpene component of the oil of black seeds (*Nigella sativa*), a frequently applied plant (*kalonji*) in traditional Indian medicine (Ayurveda, Unani), and exhibited significant antineoplastic effects [353]. Among others, polo-like kinases (Plk) were identified as tumor targets for thymoquinone [354]. Recently, a PEGylated thymoquinone nanoparticle (PEG_{4000}-TQ-Np, PEG = polyethylene glycol) with improved aqueous solubility and tumor selectivity was prepared and investigated for its anticancer properties in breast cancer cells [355]. This nanoparticle exhibited increased breast tumor cell killing and anti-migratory activity by upregulation of miR-34a and downregulation of its target Rac1 (a Rac GTPase) leading to actin depolymerisation [355].

Paeoniflorin represents a major monoterpene glucoside of the medicinal plant *Paeonia lactiflora* Pall. and blocked tumor cell invasion and metastasis (Fig. 7) [356]. Paeoniflorin also inhibited glioma cell growth (U87) and induced apoptosis in glioma cells via upregulation of miR-16 and suppressed MMP9 expression [357]. In addition, paeoniflorin showed protective effects on doxorubicin-treated cardiomyocetes via suppressed miR-1 expression and inhibition of doxorubicin-induced apoptosis in cardiomyocetes [358]. A list of microRNAs regulated by di-, sesqui- and monoterpenes is presented in Table 11.

3.2.3. Terpenoidal vitamins A, D, and E

Retinoic acid (RA, vitamin A, Fig. 8) is an essential natural diterpene for the regulation of cell growth and differentiation through binding to retinoic acid receptors (RARs) and revealed anticancer effects in various cancer models including breast, prostate, lung, liver, and pancreatic cancer [359]. In acute promyelocytic leukemia cells, retinoic acid induced the expression of several miRNAs such as let-7a-3, let-7c, miR-15a, miR-15b, miR-16-1, miR-107, miR-186, miR-215, miR-223, and miR-342, while five miRNAs (miR-17, miR-25, miR-93, miR-193, miR-181b) were suppressed after treatment with retinoic acid [360,361]. Though the inhibition of breast cancer cell growth by retinoic acid was counteracted by
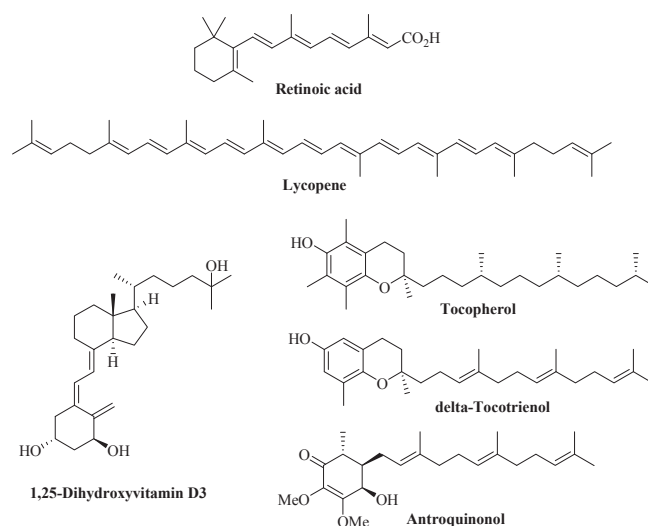
Table 11
MicroRNAs regulated or influenced by di-, sesqui- and monoterpenes.

Compound	Tumor suppressors (up-regulated)	Oncogenes (down-regulated)
Andrographolide	miR-23a-5p, miR-30b-5p, miR-106b-5p, miR-218, miR-222-3p	–
Triptolide	miR-142-3p, miR-339-5p (synergism)	–
Carnosic acid	–	miR-15b, miR-181a
Parthenolide	miR-15a, miR-16	–
Antrocin	let-7c	–
Zerumbone	miR-34	–
PEG-Thymoquinone	miR-34a	–
Paeoniflorin	miR-16	–

Fig. 8. Chemical structures of lipophilic vitamins and of their derivatives.

RA-induced expression of miR-21, RA-induced expression of miR-21 also inhibited the motility of estrogen-receptor(ER)-positive breast cancer cells (MCF-7) and suggested a beneficial effect concerning the anti-metastatic properties of retinoic acid via suppression of maspin [362]. In neuroblastoma cells (SH-SY5Y), retinoic acid induced differentiation via upregulation of miR-10a and miR-10b [363]. The SR-family splicing factor SFRS1 was identified as an important target of miR-10a and miR-10b upon treatment with retinoic acid. In addition, miR-10a and miR-10b mediated the anti-migratory and anti-metastatic activity of retinoic acid in these neuroblastoma cells [363]. In addition, retinoic acid induced neuroblastoma differentiation by upregulation of miR-9 and miR-103 associated with suppression of the expression of the differentiation inhibitor ID2 (inhibitor of DNA binding-2) [364]. In breast cancer, levels both of RARβ and of the tumor suppressor miR-10a were reduced and a positive correlation between miR-10a and RARβ was assumed [365]. Indeed, retinoic acid was able to upregulate miR-10a expression (2-fold) in breast cancer cells either alone (in SK-BR-3 cells) or in combination with thyroid hormone receptor/THRα-binding ʟ-thyroxine (in T47D cells) [365]. Retinoic acid also downregulated c-Myc and miR-130a in cancer cells leading to increased HOXA5 expression and cell death [366]. The differentiation of embryonic stem cells (ESCs) was induced by retinoic acid via suppression of miR-200b and miR-200c and of pluripotent genes such as Oct4 and Nanog [367]. Hence, in this special case the tumor suppressors miR-200b and miR-200c act as promoters of stem-cell properties such as pluripotency and immortality which can be suppressed by retinoic acid. In addition, the tumor suppressor miR-663 was upregulated by retinoic acid in leukemia cells (HL-60) leading to leukemia cell differentiation [368]. By the way, miR-10a was downregulated in these HL-60 leukemia cells after treatment with retinoic acid [368]. In glioblastoma cells, retinoic acid enhanced the anticancer effects of transfected miR-124-3p by formation of gap junctions and simplified intercellular transfer of miR-142-3p [369]. In addition, retinoic acid induced glioma cell death by induction of miR-302b leading to suppression of the transcriptional glioma growth regulator E2F3 [370]. Retinoids are derived from carotenoids and lycopene (Fig. 8) features an interesting carotenoid antioxidant from tomatoes that inhibited tumor growth [371]. In prostate cancer (PC3 cells), lycopene revealed growth inhibition and apoptosis induction via upregulation of let-7f-1 associated with suppression of Akt2 (let-7f-1 target) [372].

Table 12
MicroRNAs regulated by lipophilic vitamins and vitamin derivatives.

Compound	Tumor suppressors (up-regulated)	Oncogenes (down-regulated)
Retinoic acid	let-7a-3, let-7c, miR-9, miR-10a, miR-10b, miR-15a, miR-15b, miR-16-1, miR-21(!), miR-103, miR-107, miR-124-3p, miR-186, miR-215, miR-223, miR-302b, miR-342, miR-663	miR-17, miR-25, miR-93, miR-130a, miR-181b, miR-193, miR-200b(!), miR-200c(!)
Lycopene	let-7f-1	—
1,25-Dihydroxy-vitamin D$_3$	let-7a-2, miR-15a, miR-20b, miR-22, miR-100, miR-125b (prostate cancer), miR-181C, miR-296-3p, miR-498, miR-627	miR-17—92 cluster, miR-181a, miR-181b
Tocopherol, delta-Tocotrienol	miR-34a, miR-122a, miR-125b	—
Antroquinonol	miR-15a, miR-18a, miR-2861, miR-302b, miR-382, miR-487a, miR-760	miR-10a (lung cancer), miR-135a, miR-299-3p, miR-3126-5p, miR-3153, miR-411, miR-4321, miR-486-5p, miR-505, miR-598, miR-601, miR-939

Vitamin D and its active metabolite 1,25-dihydroxyvitamin D$_3$ (1,25-D, Fig. 8) are essential natural 9,10-*seco*-steroids that bind to the vitamin D receptor (VDR) and, thus, modulate various signaling pathways leading to cell cycle arrest (G0/G1), apoptosis and cell differentiation [373]. 1,25-D induced miR-22 expression in colon cancer cells (SW480-ADH, HCT-116) and suppressed target genes such as NELL2, OGN, HNRPH1, RERE and NFAT5 associated with anti-proliferative and anti-migratory effects of 1,25-dihydroxyvitamin D$_3$ [374]. On the other hand, 1,25-D inhibited AraC-induced apoptosis of acute myeloid leukemia cells by induction of miR-32 via Bim [375]. 1,25-D increased miR-627 expression in colon cancer models associated with suppressed JMJD1A (a histone demethylase) and growth and differentiation factor 15 leading to colon tumor growth inhibition [376]. The tumor suppressors miR-22, miR-296-3p and miR-498 were induced by 1,25-D in cervical cancer cells (SiHa) accompanied by increased Dicer expression [377]. Dicer expression was increased by 1,25-D because of the vitamin D response element in the Dicer promoter [377]. In addition, the tumor suppressor let-7a-2 was induced by 1,25-D in lung cancer cells (A549), while the tumor suppressors miR-100 and miR-125b were upregulated by 1,25-D in prostate cancer cells [378,379]. However, in MCF-7 breast cancer cells, miR-125b acted as a repressor for VDR and, thus, induced resistance to 1,25-D via reduced levels of VDR [380]. In human myeloid leukemia cells, 1,25-D suppressed miR-181a and miR-181b leading to cell cycle arrest by upregulation of p27^{KIP1} and p21^{CIP1} [381]. In addition, downregulation of the miR-17—92 cluster contributed to 1,25-D anticancer activity in NSCLC cells [382]. 1,25-D also upregulated miR-15a, miR-20b, and miR-181C in HUVECs (human umbilical vein endothelial cells) which contributed to the anti-angiogenic activity of vitamin D [383].

Tocopherol (vitamin E, Fig. 8) is a natural 6-chromanol with an isoprenoid side-chain that possesses antioxidant properties [384]. Vitamin E deficiency led to decreased levels of miR-122a and miR-125b (i.e., microRNAs involved in lipid metabolism, cancer and inflammation) in the liver of rats [385]. Downregulated miR-122a and miR-125b were observed from various cancer types and it is assumed that induction of these miRNAs contributes to the anticancer effects of tocopherol [385]. Tocotrienols are closely related to tocopherol and exhibited apoptosis induction via inhibition of signaling pathways such as PI3K/Akt and NF-κB [386]. In non-small cell lung cancer cells, delta-tocotrienol (Fig. 8) increased the expression of the tumor suppressor miR-34a leading to inhibition of Notch-1 signaling [387]. Delta-tocotrienol-induced expression of miR-34a suppressed the expression of Notch-1 and of its downstream factors (Hes-1, Cyclin-D1, Survivin, Bcl-2) associated with lung tumor cell growth inhibition, apoptosis induction and inhibition of lung cancer cell invasion [387]. Antroquinonol is a structurally related ubiquinone derivative of the camphor tree mushroom *Antrodia camphorata* which is applied in TCM for the treatment of several diseases (Fig. 8) [388]. Antroquinonol inhibited

cell growth of hepatocellular carcinoma cell lines via AMPK (AMP-activated protein kinase) activation and mTOR inhibition [389]. In non-small cell lung cancer cells, antroquinonol revealed antiproliferative activity and suppressed the expression of Bcl-2, PI3K and mTOR proteins [390]. Seven microRNAs (miR-15a, miR-18a, miR-2861, miR-302b, miR-382, miR-487a, miR-760) were upregulated in A549 lung cancer cells treated with antroquinonol, while twelve miRNAs were downregulated (miR-10a, miR-135a, miR-299-3p, miR-3126-5p, miR-3153, miR-411, miR-4321, miR-486-5p, miR-505, miR-598, miR-601, miR-939) after antroquinonol treatment [390]. A list of microRNAs regulated by terpenoidal vitamins is presented in Table 12.

4. Conclusions

Various natural phenolic and terpenoidal compounds of known anticancer activity exerted their anticancer activity via regulation of microRNAs involved in proliferation, cell death and differentiation, angiogenesis and metastasis formation. Quite a few of these natural compounds (e.g., curcumin, boswellic acid, etc.) have shown low toxicity both in animal studies and in clinical trials and appear to be suitable additives to conventional cancer therapies. In addition, the sensitivity and resistance of cancer cells to approved phenolic and terpenoidal anticancer agents such as doxorubicin, etoposide and taxol include modified expression of tumor suppressor and oncogenic miRNAs. A detailed understanding of the miRNA regulation by natural phenols and terpenes will provide essential information for improved therapy regimens including combination therapies with approved anticancer drugs or other conventional therapies associated with improved prognoses, reduced side-effects, increased quality of life of cancer patients, and breach or prevention of drug resistance.

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