



Non-coding RNA/microRNA-modulatory dietary factors and natural products for improved cancer therapy and prevention: Alkaloids, organosulfur compounds, aliphatic carboxylic acids and water-soluble vitamins



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ABSTRACT

Non-coding small RNA molecules, the microRNAs (miRNAs), contribute decisively to the epigenetic regulation processes in cancer cells. Problematic pathogenic properties of cancer cells and the response of cancers towards anticancer drugs are highly influenced by miRNAs. Both increased drug activity and formation of tumor resistance are regulated by miRNAs. Further to this, the survival and proliferation of cancer cells and the formation of metastases is based on the modulated expression of certain miRNAs. In particular, drug-resistant cancer stem-like cells (CSCs) depend on the presence and absence of specific miRNAs. Fortunately, several small molecule natural compounds were discovered that target miRNAs involved in the modulation of tumor aggressiveness and drug resistance. This review gives an overview of the effects of a selection of naturally occurring small molecules (alkaloids, organosulfur compounds, aliphatic carboxylic acids and water-soluble vitamins) on miRNAs that are closely tangled with cancer diseases.

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1. Introduction

MicroRNAs (miRNAs) feature short and highly conserved non-coding RNAs of 22–23 nucleotides and there are more than two thousand miRNAs that regulate about one-third of all human genes [1]. In fact, the regulation of important cellular processes such as proliferation, apoptosis, and differentiation of cells involves miRNAs [2]. MiRNAs also feature valuable diagnostic and prognostic factors because characteristic miRNA expression patterns were identified in tumor tissues [3–7]. The survival of drug-resistant cancer stem-like cells (CSCs) is regulated by special miRNAs as well [8,9]. MiRNAs also play an essential part concerning the formation of metastases due to regulation of epithelial-to-mesenchymal transition (EMT) of cancer cells [10,11].

The translation of target messenger RNAs (mRNAs) is blocked by

mature miRNAs via binding to the 3'-untranslated region (3'UTR) of the mRNAs [12]. Single miRNAs can target various genes while dysregulation of tumor suppressor or oncogenic miRNAs was observed in many human cancer types [13,14]. Thus, miRNAs with effects on carcinogenesis, cell proliferation and differentiation, apoptosis, and on the formation of metastasis and drug resistance feature valuable targets for the design of potent anticancer drugs [15–17]. Next generation anticancer drugs should either inhibit the activity of oncogenic miRNAs or promote the activity of tumor suppressor miRNAs. A recent review published in this journal before dealt with miRNA-modulating natural phenols and terpenoids and their effects on various tumors [18]. This review provides an overview of further anticancer active natural products (alkaloids, organosulfur and aliphatic carboxylic acid derivatives, water-soluble vitamins) and their manifold and versatile interactions with miRNAs involved in cancer diseases.

2. Dietary compounds and natural products (alkaloids, organosulfur compounds, aliphatic carboxylic acids and water-soluble vitamins) with effects on miRNA expression and activity

Nature provides us with a plethora of drug candidates we only

Abbreviations: AM, allyl mercaptan; AOM, azoxymethane; CPT, camptothecin; DADS, diallyl disulfide; DHA, docosahexaenoic acid; DIM, 3,3'-diindolylmethane; EPA, eicosapentaenoic acid; FA, folic acid; GTC, green tea catechins; I3C, indole-3-carbinol; NaB, sodium butyrate; PEITC, phenethylisothiocyanate; PUFA, polyunsaturated fatty acid; SAMC, S-allylmercaptocysteine; SFN, sulforaphane; TSA, trichostatin A.

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need to explore. In order to develop potent agents against deadly diseases such as cancer, it is necessary to investigate the modes of action of these dietary and natural products thoroughly. There are very promising derivatives from the natural compound classes of alkaloids, organosulfur compounds, aliphatic carboxylic acids and water-soluble vitamins. Their multiple modes of action and their manifold interactions with miRNAs represent the key issues of this review manuscript.

2.1. Alkaloids

Alkaloids feature a rich compound class (ca. 12.000 alkaloids were investigated as bioactive compounds) comprising small molecule natural amines and *N*-heterocyclic natural products [19]. Several alkaloids have shown potent anticancer activity and some of them (e.g., Vinca alkaloids, camptothecins) have already been approved for chemotherapy of certain cancer and leukemia diseases, while others (e.g., DIM, berberine, vitamin C) seem to be valuable additives for chemotherapeutic regimens. The interactions of anticancer active alkaloids subdivided into indole alkaloids on the one hand, and quinoline, isoquinoline and quinolizidine alkaloids on the other hand, are presented in this chapter.

2.1.1. Indole alkaloids

Indole-3-carbinol was detected in various *Brassica* vegetables (e.g., broccoli, cabbage, cauliflower, sprouts) and its condensation product 3,3'-diindolylmethane (DIM) is generated after consumption in the stomach under acidic conditions (Fig. 1) [20]. The more stable compound DIM revealed distinct anticancer activities via suppression of the PI3K-Akt-mTOR signaling pathway and via inhibition of epigenetic factors such as DNA-methyl transferases/DNMTs (hypomethylation) and histone deacetylases (HDACs) [21,22]. Several clinical trials of I3C and DIM have revealed that both I3C and DIM were well tolerable and further trials with DIM in prostate cancer patients, in patients with cervical dysplasia and as preventive agent in healthy non-smokers are ongoing [23]. DIM (more precisely, formulated DIM called BR-DIM with improved bioavailability) increased the expression of tumor suppressing let-7 miRNAs associated with suppression of the let-7-target EZH2 (a histone-lysine *N*-methyltransferase) and inhibition of prostate tumor growth (LNCaP, C4-2B, PC-3) [24]. In pancreatic cancer cells (Colo357, Panc-1), DIM induced miR-146a expression leading to suppression of EGFR (epidermal growth factor receptor), IRAK-1 (interleukin 1 receptor-associated kinase 1), NF- κ B (nuclear factor κ B) and MTA2 (metastasis-associated protein 2) and to inhibition of cancer cell invasion [25]. DIM also upregulated let-7b/c/d/e and miR-200b/c in gemcitabine-resistant pancreatic cancer cells (Mia-PaCa-2) causing a reversal of the EMT (epithelial-to-mesenchymal

transition) via suppression of ZEB1 (zinc finger E-box binding homeobox 1), slug and vimentin and upregulation of E-cadherin [26]. In combination with Herceptin, DIM increased miR-200 expression accompanied by FoxM1 suppression and induction of apoptosis in HER-2 positive breast cancer cells (SKBR3, MDA-MB-468) [27]. DIM also induced miR-34 expression in castrate-resistant prostate cancer cells associated with inhibition of Notch-1 and androgen receptor (AR) signaling and lowered the self-renewal potential of prostate cancer cells [28]. In breast cancer models (T47D, MDA-MB-231), DIM increased the expression of the miRNA cluster miR-212/132 via activation of the aryl hydrocarbon receptor (Ahr) leading to the suppression of the pro-metastatic protein Sox4 (SRY-related HMG-box 4) both *in vitro* and *in vivo*, to reduced tumor growth and to inhibition of metastasis formation [29].

Concerning oncogenic miRNAs (oncomiRs), I3C suppressed miR-21 expression in pancreatic cancer cells (Panc-1) leading to upregulation of the miR-21 target PDCD4 (programmed cell death protein 4) and enhanced gemcitabine-sensitivity of the I3C-treated cancer cells [30]. In vinyl carbamate-induced lung cancer, I3C was able to suppress the upregulated miRNAs miR-21, miR-31, miR-130a, miR-146b, and miR-377 [31]. In addition, DIM down-regulated miR-221 in pancreatic cancer cells (MiaPaCa-2, Pan377 c-1) associated with upregulation of the miR-221 targets PTEN (phosphatase and tensin homolog deleted on chromosome 10), PUMA (p53 upregulated modulator of apoptosis), and the CDK(cyclin-dependent kinase)-inhibitors p27 and p57 [32]. Interestingly, DIM revealed inhibitory effects on bone metastasis formation by prostate cancers via suppression of miR-92 [33]. Surprisingly, DIM enhanced the expression of miR-21 in breast cancer cells leading to degradation of Cdc25A and cancer cell growth inhibition [34]. Thus, in this special case miR-21 can also function as a tumor suppressor. A list of miRNAs regulated by DIM and I3C is shown in Table 1.

Tubulin-binding Vinca alkaloids (e.g., vinblastine, vincristine) were first isolated from the Madagascar periwinkle (*Catharanthus roseus*) in the 1960's and feature complex indole alkaloids which represent valuable and approved anticancer drugs for the treatment of advanced cancer diseases (Fig. 2) [35]. The semi-synthetic Vinca alkaloid vinorelbine (Fig. 2) revealed an improved toxicity profile compared with vinblastine and vincristine. Due to clinical drawbacks such as emerging multidrug-resistance upon treatment with Vinca alkaloids, the role of miRNAs for the induction of resistance to Vinca alkaloids was investigated in various cancer models. In breast cancer cells, miR-27a and miR-451 induced expression of the ABC-transporter MDR1/Pgp, and suppression of miR-27a and miR-451 was accompanied by increased accumulation of vinblastine in cancer cells [36]. Similar results were observed from MCF-7 breast cancer cells, where vinblastine suppressed the expression of miR-27a, miR-27b, miR-324-3p, miR-328, miR-148a and miR-451, while these miRNAs were not affected by vinblastine in colon cancer cells (Caco-2) [37]. In particular, the down-regulation of miR-27b, miR-148a, and miR-451 by vinblastine was associated with increased expression of ABC-transporters such as ABCB1 and ABCC1 leading to enhanced drug efflux from the cancer cell [38]. MiR-34a expression enhanced the antiproliferative activity of vincristine in retinoblastoma cells by suppression of HMGB1 (high mobility group box 1) [38]. Vincristine-resistant hepatocellular carcinoma (HCC) cells exhibited upregulated miRNAs such as miR-27b, miR-181a, miR-146b-5p, miR-181d and miR-146a [39]. In addition, vincristine-resistant laryngeal cancer cells (Hep-2/v) exhibited increased expression of miR-210 and miR-923, while five miRNAs were suppressed (miR-93, miR-93*, miR-424*, miR-25*, miR-494) [40]. Overexpression of the oncogenic miR-125b in Ewing sarcoma cells decreased the anticancer activity of vincristine [41]. R-CHOP (rituximab, cyclophosphamide, adriamycin,

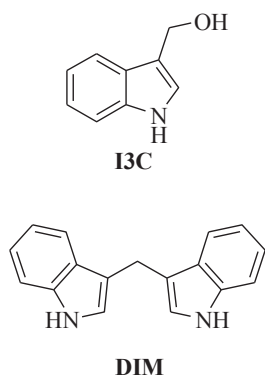


Fig. 1. Structures of the indole alkaloids I3C and DIM.

Table 1
Regulation of microRNAs by DIM and I3C.

Compound	Tumor suppressors (up-regulated)	Oncogenes (down-regulated)
DIM	let-7b/c/d/e [24,26], miR-21(!) [34], miR-34 [28], miR-146a [25], miR-200b/c [27], miR-212/132 cluster [29]	miR-92 [33], miR-221 [32]
I3C	–	miR-21 [31], miR-31 [31], miR-130a [31], miR-146b [31], miR-377 [31]

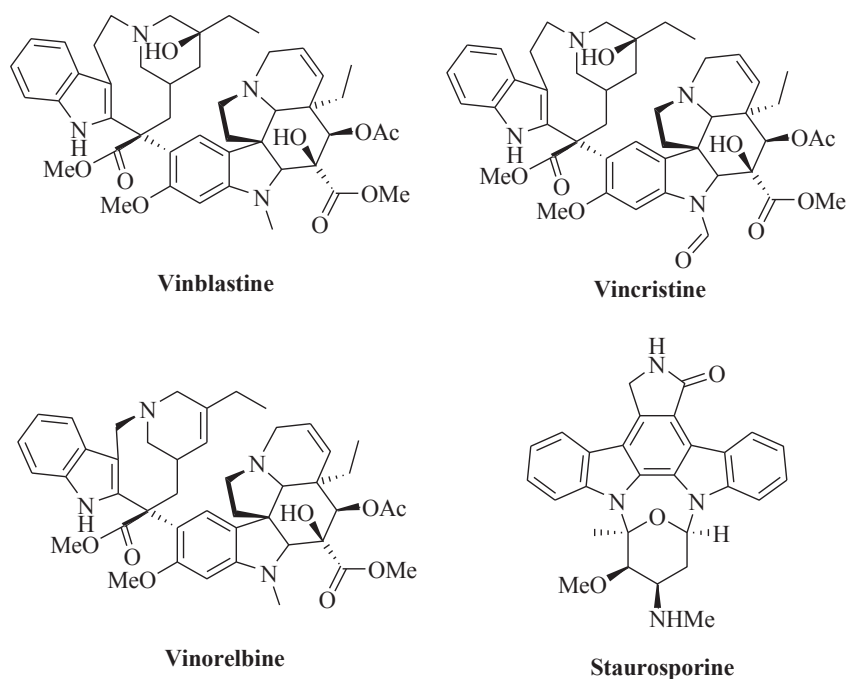


Fig. 2. Structures of the Vinca alkaloids and staurosporine.

vincristine, prednisone) is clinically approved for the treatment of diffuse large B-cell lymphoma (DLBCL) and DLBCL-patients with high miR-224 levels (associated with low CD59 expression) responded better to R-CHOP treatment (longer overall survival and progression free survival) than patients with low miR-224 expression [42]. Key components of R-CHOP such as vincristine showed increased anticancer activity in DLBCL cells overexpressing miR-199a or miR-497, and expression of miR-199a and miR-497 led to prolonged overall survival of DLBCL patients [43]. 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 the anti-proliferative effects of vinorelbine and of another tubulin targeting drug (paclitaxel) in H1993 non-small cell lung cancer cells (=NSCLC cells) significantly [44]. In vinorelbine-resistant MDA-MB-231/Nvb breast cancer cells, four miRNAs (miR-138-5p, miR-140-3p, miR-210-3p and miR-3613-5p) were upregulated both in the cancer cells and in the exosomes [45]. It is assumed that drug resistance can be transmitted to other cancer cells via exosomes loaded with oncogenic miRNAs. MAPK, mTOR, Wnt and TGF- β signaling pathways contributed to vinorelbine-resistance in resistant MDA-MB-231/Nvb breast cancer cells via dysregulated miRNA expression [46]. Eleven miRNAs (miR-138-5p, miR-182-5p, miR-18a-5p, miR-193b-3p, miR-199a-5p, miR-210-3p, miR-21-5p, miR-378a-3p, miR-4262, miR-4725-5p, and miR-92b-3p) were upregulated while 6 miRNAs were downregulated (let-7a-5p, miR-130a-3p, miR-146a-5p, miR-221-3p, miR-23b-3p, and miR-4319) in vinorelbine-resistant breast cancer cells [46]. Patients suffering from NSCLC treated with a combination of vinorelbine and cisplatin

were examined for prognostic miRNA markers and the microRNAs miR-149 and miR-375 were found predictive for response to the combination treatment and progression free survival [47]. In addition, four other miRNAs (miR-29c, miR-124, miR-200c, and miR-424) were applied as a signature for overall survival of NSCLC patients treated with cisplatin-vinorelbine [47].

The indole alkaloid staurosporine features a natural pan-kinase inhibitor and the prototype for the design of more selective protein kinase inhibitors approved for clinical application as anticancer agents (Fig. 2) [48]. Staurosporine induced apoptosis in proliferating human cells and overexpression of miR-31 augmented the apoptosis induction by staurosporine via downregulation of PKC ϵ and Bcl-2 in MCF10A breast epithelial cells [49]. In Wi38 fibroblast cells, staurosporine-induced apoptosis was mediated by functional miR-34 in a p53-dependent way and suppression of miR-34 reduced apoptosis induction by staurosporine due to upregulation of Bcl-2 [50]. In addition, apoptosis induction by staurosporine was mediated by expression of miR-145 leading to inhibition of DFF45 (DNA fragmentation factor-45) [51]. In contrast to that, miR-125b expression suppressed apoptosis induction by staurosporine via downregulation of pro-apoptotic Bmf and KLF13 in MPP (multipotent progenitor) cells and Jurkat T-cell leukemia cells [52]. Suppression of miR-24 potentiated the apoptosis induction by staurosporine in prostate cancer cells via upregulation of pro-apoptotic FAF1 (Fas associated factor 1) [53]. Table 2 shows a list of miRNAs involved in sensitivity or resistance to indole alkaloids such as Vinca alkaloids and staurosporine.

Anticancer agents that bind covalently to nucleotides likely

Table 2
Influence of microRNAs on cellular sensitivity or resistance to Vinca alkaloids and staurosporine.

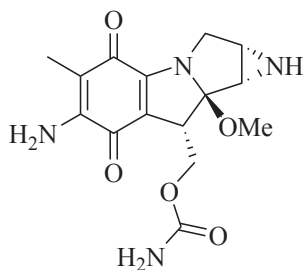
Compounds	Sensitivity	Resistance
Vinblastine	–	miR-27a [36,37], miR-27b [37], miR-148a [37], miR-324-3p [37], miR-328 [37], miR-451 [36,37]
Vincristine	miR-25* [40], miR-34a [38], miR-93 [40], miR-93* [40], miR-199a [43], miR-224 [42], miR-424* [40], miR-494 [40], miR-497 [43]	miR-27b [39], miR-125b [41], miR-146a [39], miR-146b-5p [39], miR-181a [39], miR-181d [39], miR-210 [40], miR-923 [40]
Vinorelbine	let-7a-5p [46], miR-23b-3p [46], miR-130a-3p [46], miR-146a-5p [46], miR-149 [47], miR-221-3p [46], miR-375 [47], miR-4319 [46]	miR-18a-5p [46], miR-21-5p, miR-92b-3p [46], miR-133a/b [44], miR-138-5p [45,46], miR-140-3p [45], miR-182-5p [46], miR-193b-3p [46], miR-199a-5p [46], miR-210-3p [45,46], miR-361-3p [44], miR-378a-3p [46], miR-3613-5p [45], miR-4262 [46], miR-4725-5p [46]
Staurosporine	miR-31 [49], miR-34 [50], miR-145 [51]	miR-24 [53], miR-125b [52]

modulate the expression and activity of oligonucleotides such as non-coding RNAs and miRNAs as well. The indole alkaloid and approved anticancer drug mitomycin C was initially isolated from *Streptomyces castiposus* and causes DNA damage via mono- and bifunctional alkylations (formation of cross-links) (Fig. 3) [54,55]. Alkylation of nucleobases (guanine-N2) by mitomycin C requires the activation of mitomycin C via enzymatic reduction (e.g., by DT-diaphorase) of its quinone ring system [56]. In urothelial bladder cancer (UBC) cells, miR-31 served as a tumor suppressor and sensitized UBC cells to mitomycin C via direct suppression of ITGA5 (integrin $\alpha 5$) and inhibition of Akt and ERK signaling [57]. MiR-31 also increased the tumor growth inhibitory activity of mitomycin C *in vivo* in UBC xenografts (T24) [57]. However, the nucleotide binding properties of alkylating agents such as mitomycin C harbor the danger of long-term genotoxicity and of inheritable aberration of miRNA expression leading to new cancer diseases as side-effects [58]. Indeed, treatment of HeLa cells with mitomycin C revealed increased inherited expression of five oncogenic miRNAs (miR-19b-3p, miR-21-3p, miR-30a-3p, miR-30e-3p, miR-182-5p) and inherited downregulation of nine tumor suppressor miRNAs (miR-23b-3p, miR-29b-3p, miR-99a-5p, miR-99b-5p, miR-100-5p, miR-148a-3p, miR-193a-3p, miR-340-5p, miR-365a-3p) [58].

2.1.2. Quinoline, isoquinoline and quinolizidine alkaloids

The anticancer active quinoline alkaloid camptothecin (CPT) was isolated from the Chinese tree *Camptotheca acuminata* [59]. CPT and its water-soluble derivatives topotecan and irinotecan represent important approved anticancer drugs for the treatment of various hematological malignancies and solid tumor diseases (Fig. 4) [60]. CPT and its derivatives induce apoptosis by inhibition of topoisomerase 1 (Top1) and stabilization of the Top1-DNA cleavage complex leading to toxic DNA damage [61]. The connection between CPT activity and miRNA expression was investigated. For instance, downregulation of oncogenic miR-125b was observed in apoptotic cancer cells upon treatment with CPT [62]. MiR-125b-

mediated mitochondrial apoptotic pathways were induced by CPT associated with increased expression of the pro-apoptotic factors Bak1, Mcl1, and p53 [62]. In line with these findings, the ectopic expression of miR-125b blocked apoptosis induction by CPT [62]. In contrast to that, overexpression of the tumor suppressing miRNAs miR-15a and miR-16 sensitized HeLa cervical carcinoma cells to CPT treatment and enhanced autophagy in HeLa cells via suppression of Rictor, a component of the mTORC2 complex, followed by the inhibition of phosphorylation of mTORC1 and p70S6K [63]. CPT derivatives modulated the response of glioma cells to hypoxia and the connection between HIF-1 (hypoxia-inducible factor 1) and microRNAs upon treatment with CPT was investigated [64,65]. Indeed, CPT upregulated the expression of miR-155 and miR-17-5p leading to inhibitory effects on HIF-1 α expression and activity in hypoxic HeLa cancer cells [65]. In colorectal cancer stem cells, the upregulation of miR-451 reduced resistance to the water-soluble CPT derivative irinotecan associated with suppression of Wnt-signaling and COX-2 (cyclooxygenase 2) expression as well as downregulation of the ABC-transporter ABCB1 (which eliminates intracellular irinotecan molecules) [66]. The activity of irinotecan was increased by suppressed miR-21 expression in gastric cancer and low miR-21 expression resulted into irinotecan-sensitivity [67]. The expression of the multidrug resistance mediating ABC transporter ABCG2 is regulated by miR-519c and irinotecan-resistant colorectal cancer showed low levels of miR-519c but high levels of ABCG2 [68]. In HCC cells, overexpression of miR-23a induced irinotecan-resistance via downregulation of topoisomerase 1 expression [69]. In patients suffering from metastatic colorectal cancer, the appearance of single-nucleotide polymorphisms (SNPs) in the miR-26a-1 gene and in the 5'UTR of pre-miR-100 led to prolonged overall survival and progression-free time when treated with a combination of 5-FU (5-fluorouracil) and irinotecan [70]. In addition, the efficacy of anti-EGFR therapy (cetuximab) in combination with irinotecan was distinctly enhanced in a group of KRAS-mutated, chemotherapy-refractory colorectal cancer patients with high let-7a levels accompanied by improved survival which paves the way for new therapy options in these cases [71]. In addition, high levels of miR-345 were correlated with resistance to irinotecan plus cetuximab 3rd line treatment in colorectal cancer patients and in non-KRAS mutant patient sub-groups [72]. Across the panel of the NCI-60 cell lines, topotecan and irinotecan suppressed miR-24 expression, while upregulation of miR-24 decreased Top1 sensitivity to Top1 poisons [73]. In breast cancer cells (MCF-7), oncogenic miR-21 was involved in topotecan-resistance and downregulation of miR-21 re-sensitized breast cancer cells to topotecan [74]. In addition, the modulation of miRNAs associated with drug resistance in 16 ovarian cancer cell lines upon treatment with topotecan was investigated [75]. Three microRNAs (miR-34b, miR-431, miR-518c-AS) were upregulated by topotecan treatment, while miR-142-5p was downregulated by topotecan in drug resistant ovarian cancer cells [75].



Mitomycin C

Fig. 3. Chemical structure of mitomycin C.

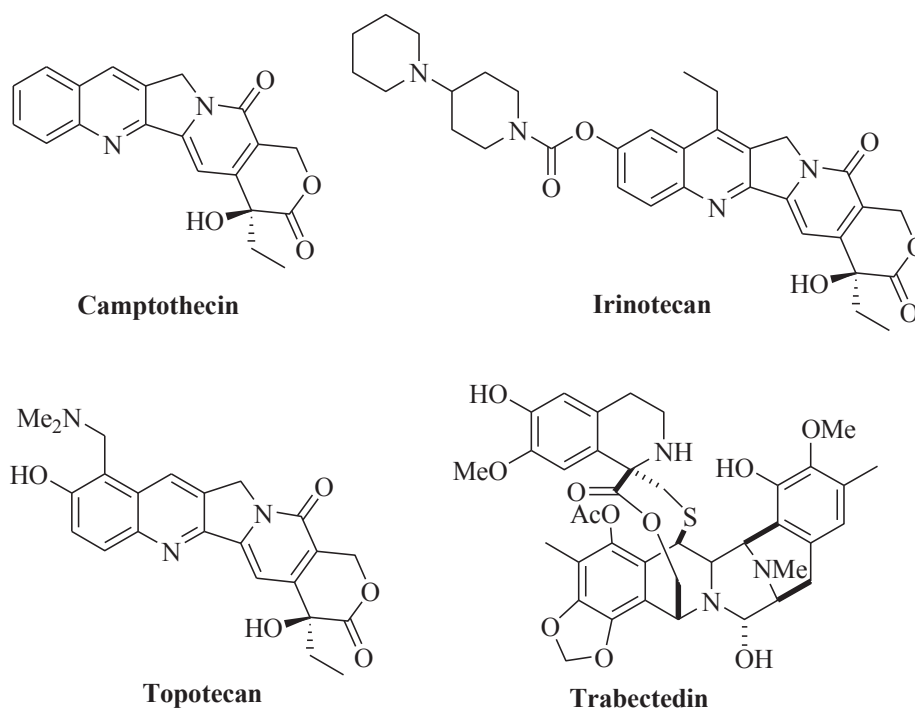


Fig. 4. Chemical structures of camptothecin derivatives and trabectedin.

The natural compound trabectedin (Ecteinascidin 743, Yondelis[®]) represents an alkylating tetrahydroisoquinoline alkaloid initially isolated from the tunicate *Ecteinascidia turbinata* of the Caribbean Sea, which is the host of the trabectedin-forming bacterial symbiont *Endoecteinascidia frumentensis* (Fig. 4) [76]. Trabectedin exhibited strong cytotoxic activity against various tumors and was approved for the therapy of soft tissue sarcoma and ovarian cancer [76]. Trabectedin damages DNA by a unique mechanism, the trabectedin molecule binds to nitrogen-N2 of guanine bases of the DNA minor groove which causes a bended DNA molecule followed by interaction with DNA binding proteins of the TC-NER (transcription-coupled nucleotide excision repair) DNA-repair system leading to cell death in the end via formation of double strand breaks in particular in HR(homologous recombination)-deficient cells [76]. In addition, trabectedin inhibited the transcription activity of FUS-CHOP in sensitive myxoid liposarcoma (MLS) [77]. Facing the influence of trabectedin on transcription, D'Incalci and coworkers investigated the effects of trabectedin on miRNA expression in MLS cells (402-91 sensitive and 402-91/ET trabectedin-resistant MLS cells) [78]. In the trabectedin-resistant cells, the tumor suppressor let-7e was suppressed (three-fold) and oncogenic miR-21 was upregulated (two-fold) when compared with the sensitive MLS cells which was consequently accompanied by the upregulation of let-7e targets (CCDN1, SEMA4C, E2F5) and suppression of miR-21 targets (PDCD4) in the resistant cells [78]. In addition, the tumor suppressors miR-192, miR-130a and miR-98 were downregulated in 402-91/ET

cells, while oncogenic miR-7 was induced. The genes of the miRNAs miR-7, miR-21 and miR-130a harbor CHOP-binding motifs in their promoters and, thus, are probably modulated by trabectedin in a FUS-CHOP dependent way [78]. A list of miRNAs involved in drug resistance or sensitivity to camptothecins and trabectedin is shown in Table 3.

The isoquinoline alkaloid berberine features a quaternary cationic quinolinizinium derivative found in various medicinal plants such as *Berberis aristata*, *Coptis chinensis* and *C. japonica*, *Phellodendron amurense* and *P. chinense* (Fig. 5) [79]. Berberine induces cytotoxic effects in cancer cells by interaction with DNA leading to double-strand breaks, telomerase inhibition by triplex and G-quadruplex formation and stabilization of the topoisomerase-DNA “cleavable complex” [79]. In multiple myeloma cells (U266), berberine induced apoptosis via suppression of oncogenic miR-21 and anti-apoptotic Bcl-2, and via inhibition of NF- κ B translocation [80]. Berberine-mediated suppression of miR-21 in multiple myeloma cells was associated with upregulation of PDCD4 expression [81]. It is assumed that berberine inhibits miR-21 expression via suppression of IL6 (interleukin 6) and STAT3 (signal transducer and activator of transcription) [81]. In addition, berberine sensitized ovarian cancer cells (SKOV3) to cisplatin treatment via suppression of miR-21 and increased expression of the tumor suppressor PDCD4 [82].

During the processing of the precursor miRNA hairpin a miRNA duplex is formed that consists of a guide strand (termed miRNA) that forms the miRISC complex upon binding to Argonaute (AGO),

Table 3

Influence of microRNAs on cellular sensitivity or resistance to camptothecin derivatives and to trabectedin.

Compounds	Sensitivity	Resistance
Camptothecin	miR-15a [63], miR-16 [63]	miR-125b [62]
Irinotecan	let-7a [71], miR-451 [66], miR-519c [68]	miR-21 [67], miR-23a [69], miR-24 [73], miR-345 [72]
Topotecan	miR-124-5p [75]	miR-21 [74], miR-24 [73], miR-34b [75], miR-431 [75], miR-518c-AS [75]
Trabectedin	let-7e [78], miR-98 [78], miR-130a [78], miR-192 [78]	miR-7 [78], miR-21 [78]

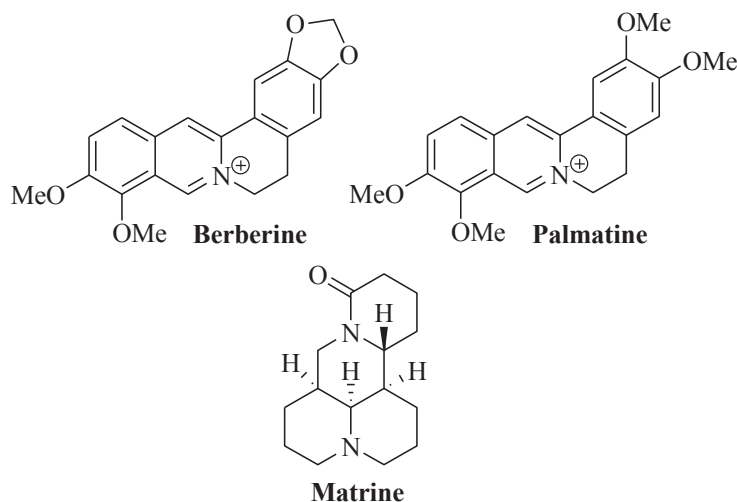


Fig. 5. Structures of berberine, palmatine and matrine.

and a passenger strand (termed miRNA*) that was initially believed to be non-functional in most cases and to be degraded soon. However, the passenger strand leading to miR-21* (=miR-21-3p) plays an important role for the regulation of cell growth as well. In hepatocellular carcinoma cells (HepG2), berberine increased the levels of miR-21-3p associated with tumor growth inhibition and apoptosis induction [83]. It was shown that miR-21-3p acted as a tumor suppressor in the hepatoma cells and directly inhibited the expression of the methionine adenosyltransferases MAT2A and MAT2B accompanied by increased SAM (*S*-adenosyl-methionine) levels as a mechanism of the anti-hepatoma activity of miR-21-3p and berberine [83]. Berberine also significantly suppressed the miRNA clusters miR-99a–125b, miR-17–92 and miR-106–25 in multiple myeloma cells [84]. In particular, downregulation of the oncogenic miR-99a–125b cluster by berberine (mediated by modulation of p53, Erb and MAPK signaling pathways) induced apoptosis and cell cycle arrest in the G2-phase in multiple myeloma cells [84].

Palmatine features another isoquinoline alkaloid of the roots of *Coptis japonica* whose chemical structure is closely related to berberine (Fig. 5) [85]. Palmatine revealed anticancer activity against prostate cancer cells by inhibition of NF- κ B [86]. In breast cancer cells (MCF-7), the expression of the tumor suppressor miR-200c was increased after treatment with palmatine chloride leading to ZEB1 inhibition and E-cadherin upregulation [87]. In addition, palmatine chloride induced the expression of the tumor suppressors miR-34a and miR-141 in MCF-7 breast cancer cells [87].

The quinolizidine alkaloid matrine was isolated from *Sophora flavescens* and exhibited strong anticancer activity (Fig. 5) [88]. In breast cancer cells, matrine induced cell cycle arrest and apoptosis

via suppression of oncogenic miR-21 and inhibition of Akt signaling as well as upregulation of PTEN (phosphatase and tensin homolog) [88]. Matrine also modulated miRNA levels in gastric cancer cells and suppressed the expression of 20 oncomirs overexpressed in gastric cancer cells including let-7b-5p, miR-10a-5p, miR-15b-5p, miR-18a-5p, miR-19a-3p, miR-19b-3p, miR-20b-5p, miR-21-5p, miR-23a-3p, miR-26b-5p, miR-27a-3p, miR-27b-3p, miR-32-5p, miR-34a-5p, miR-98, miR-106b-5p, miR-181a-5p, miR-183-5p and miR-338-3p [89]. A list of miRNAs regulated by isoquinoline and quinolizidine alkaloids is shown in Table 4.

2.2. Organosulfur-based natural products

Organosulfur-based natural products include sulfides and isothiocyanates that occur in *Allium* species (garlic) and in cruciferous vegetables (e.g., broccoli, watercress) and revealed distinct epigenetic effects in cancer cells [90]. The natural garlic disulfide diallyl disulfide (DADS, Fig. 6) is usually metabolized to *S*-allylmercaptocysteine (SAMC) and to allyl mercaptan (AM) and exhibited tumor cell growth inhibition, apoptosis induction as well as inhibition of metastasis formation and angiogenesis [91,92]. DADS and to a greater extent its metabolite AM strongly inhibited histone deacetylases (HDACs) [93,94]. In gastric cancer cells (MGC-803), DADS inhibited cell growth and induced apoptosis via induction of miR-200b and miR-22 expression leading to inhibition of Wnt-1 signaling [95]. In addition, the expression of the tumor suppressors miR-200b and miR-22 enhanced the growth inhibitory activity and the anticancer effects of DADS both *in vitro* and *in vivo* [95]. DADS also inhibited breast cancer proliferation and metastasis formation by upregulation of the tumor suppressor miR-34a associated with blocked Src/Ras/ERK signaling (with the Src gene as a

Table 4
Regulation of microRNAs by isoquinoline and quinolizidine alkaloids.

Compounds	Tumor suppressors (up-regulated)	Oncogenes (down-regulated)
Berberine	miR-21-3p [83]	miR-21 [80], miR-99a-125b cluster [84], miR-17-92 cluster [84], miR-106-25 cluster [84]
Palmatine chloride	miR-34a [87], miR-141 [87], miR-200c [87]	–
Matrine	–	let-7b-5p [89], miR-10a-5p [89], miR-15b-5p [89], miR-18a-5p [89], miR-19a-3p [89], miR-19b-3p [89], miR-20b-5p [89], miR-21 [88], miR-21-5p [89], miR-23a-3p [89], miR-26b-5p [89], miR-27a-3p [89], miR-27b-3p [89], miR-32-5p [89], miR-34a-5p [89], miR-98 [89], miR-106b-5p [89], miR-181a-5p [89], miR-183-5p [89], miR-338-3p [89]

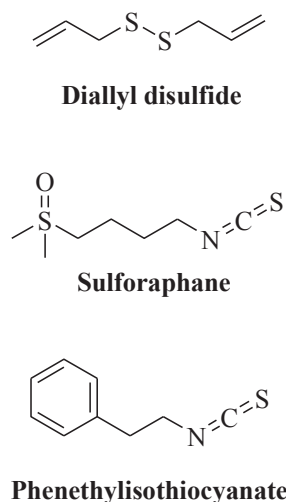


Fig. 6. Structures of natural organosulfur compounds.

direct target of miR-34a) [96]. In gastric cancer cells (SGC-7901), DADS-mediated induction of miR-34a suppressed the PI3K/Akt signaling pathway and successfully blocked cancer cell invasion while apoptosis was strongly induced in DADS-treated cells [97].

Sulforaphane (SFN) features an isothiocyanate derivative of cruciferous vegetables, which inhibits carcinogenesis as well as tumor growth *in vivo* (Fig. 6) [98]. In the plants, isothiocyanates with strong effects on various epigenetic mechanisms occur as more stable glucosinolate prodrugs that release the reactive isothiocyanate agent upon consumption catalyzed by the enzyme myrosinase [99]. SFN itself induced cell cycle arrest via p21 activation and inhibited HDAC enzymes such as HDAC6 [90]. In bladder cancer cells (T24), SFN induced the expression of the tumor suppressor miR-200c associated with blocked EMT and inhibition of metastasis formation [100]. Similar effects (miR-200c upregulation, suppression of cancer stemness) were observed from oral squamous cell carcinomas after treatment with SFN [101]. In addition, miR-140 was upregulated by SFN in breast cancer cells (MCF10DCIS, and MDA-MB-231) leading to the suppression of SOX9 and aldehyde dehydrogenase 1 (ALDH1) [102]. The combination of SFN with green tea catechins (GTCs) was much more anticancer active against advanced pancreatic cancer than GTCs alone because of the SFN-mediated increased expression of the tumor suppressor let-7a leading to K-Ras inhibition [103]. In non-malignant colon epithelial cells (NCM460, NCM356), SFN suppressed three miRNAs (miR-633, miR-155, miR-106a*) while 15 miRNAs (miR-372, miR-342-3p, miR-486-5p, miR-9, miR-9*, miR-145, miR-146a, miR-629, miR-505, miR-758, miR-30*, miR-27b*, miR-135*, miR-27b, miR-23b) were upregulated by SFN which was associated with a reduced risk of colon cancer development [104].

The closely related isothiocyanate phenethylisothiocyanate (PEITC) from watercress exhibited enhanced histone acetylation

accompanied by p21 induction in prostate cancer cells (Fig. 6) [105]. Indeed, PEITC suppressed the oncogenic high-risk factor miR-141 in prostate cancer cells (LNCaP) leading to increased expression of the miR-141-target Shp (small heterodimer partner protein, a small orphan receptor and corepressor) and suppressed androgen receptor (AR) signaling [106]. In order to examine the chemopreventive effects of PEITC, rats exposed to cigarette smoke were treated with PEITC and a strong reversal of smoke-induced miRNA suppression was observed in the lungs of the PEITC-treated rats. These PEITC-induced miRNAs include miR-125b (stress response), miR-26a (TGF- β expression), miR-146-prec (NF- κ B activation), let-7a and let-7c (Ras activation, cell proliferation and angiogenesis), miR-192 (Ras activation), miR-222-prec and miR-123-prec (cell proliferation and angiogenesis) [107]. It is assumed that PEITC is able to modulate carcinogen metabolism leading to enhanced inactivation and excretion of cigarette/tobacco smoke carcinogens [107]. A list of miRNAs regulated by dietary organosulfur compounds is given in Table 5.

2.3. Natural aliphatic carboxylates

The simple aliphatic short-chain carboxylic acid butyric acid, which was initially isolated from glycerol esters of butter, and its sodium salt, sodium butyrate (NaB), were identified as non-competitive pan-HDAC inhibitors (inhibition of class I and II HDAC enzymes) with modulatory effects on microRNA expression (Fig. 7) [108,109]. In colorectal cancer cells (HCT-116), high doses of NaB (1–2 mM) downregulated the oncogenic clusters miR-17-92, miR-106a-363 and miR-106b-25 as well as miR-34a, miR-222-5p, miR-7, miR-221, miR-886, let-7b-3p, and miR-196b leading to p21 induction [110]. Several miRNAs were upregulated in colorectal cancer cells upon treatment with NaB (miR-96, miR-183, miR-487b, miR-381, miR-300, miR-215, miR-194, miR-874, miR-602, miR-95, miR-320b, miR-492, miR-583, miR-184, miR-202, miR-1908, miR-637, miR-424) [110]. NaB also downregulated the oncogenes miR-135a and miR-106b in colon adenoma cells accompanied by upregulation of p21 [111]. The tumor suppressors miR-15a and miR-16-1 were upregulated by NaB in lung cancer cells (A549, H1299) [112]. In addition, the expression of miR-101, miR-143 and miR-145 was induced by NaB in Burkitt's lymphoma cells (Raji) associated with suppression of PI3K/Akt signaling and inhibition of tumor cell growth [113]. In combination with VP-16, NaB suppressed methylation of the p16^{INK4a} promoter in Burkitt's lymphoma cells [113]. NaB also induced miR-125a-5p expression in breast cancer stem cells leading to increased apoptosis of breast cancer cells [114]. In breast cancer cells (MDA-MB-231, MCF-7), NaB induced cellular senescence via increased expression of miR-31 leading to suppression of BMI1 [115]. Because of the low bioavailability of NaB, NaB prodrugs such as AN-9 (Pivanex, pivaloyloxymethyl butyrate) and tributyrin (tributyril glyceride) were developed which showed improved biological activities and pharmacokinetics [116,117].

The natural hydroxamic acid trichostatin A (TSA) represents an antifungal antibiotic able to inhibit HDACs of the classes I and II

Table 5
Regulation of microRNAs by natural organosulfur derivatives.

Compounds	Tumor suppressors (up-regulated)	Oncogenes (down-regulated)
Diallyl disulfide	miR-22 [95], miR-34a [96,97], miR-200b [95]	–
Sulforaphane	let-7a [103], miR-9 [104], miR-9* [104], miR-23b [104], miR-27b [104], miR-27b* [104], miR-30* [104], miR-135* [104], miR-140 [102], miR-145 [104], miR-146a [104], miR-200c [100,101], miR-342-3p [104], miR-372 [104], miR-486-5p [104], miR-505 [104], miR-629 [104], miR-758 [104]	miR-106a* [104], miR-155 [104], miR-633 [104]
PEITC	let-7a [107], let-7c [107], miR-26a [107], miR-123-prec [107], miR-125b [107], miR-146-prec [107], miR-192 [107], miR-222-prec [107]	miR-141 [106]

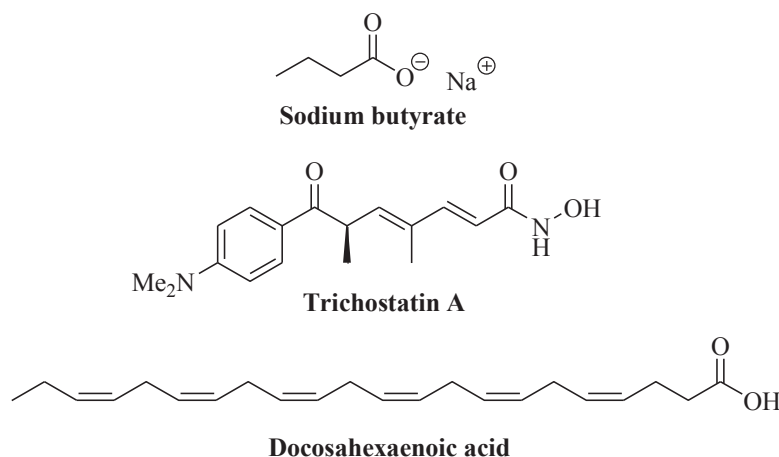


Fig. 7. Structures of sodium butyrate, trichostatin A and docosahexaenoic acid.

(Fig. 7) [118]. The hydroxamate moiety of TSA coordinates to the catalytic zinc ion of the active site of class I and class II HDAC enzymes leading to HDAC inhibition and hyperacetylation of histones and of other HDAC targets in the TSA-treated cells [119]. TSA reduced the expression of the oncogenic miR-106b-93-25 cluster via MYC downregulation in endometrial cancer cells [120]. On the other hand, TSA induced the expression of the tumor suppressor miR-7 leading to EGFR suppression in triple-negative breast cancer cells [121]. TSA-mediated upregulation of miR-125a-5p led to enhanced apoptosis induction in breast cancer cells [122]. The miRNA profile of apoptosis-resistant breast cancer cells was modified by TSA, i.e., the oncomirs miR-500 and miR-645 were downregulated by TSA, and the tumor suppressors miR-1, miR-22, miR-139, miR-143, miR-144, miR-153, miR-191*, miR-194, miR-202*, miR-215, miR-335, miR-486 and miR-559 were upregulated by TSA [123]. Oncogenic miR-155 was also upregulated by TSA-treated breast cancer cells and combination of TSA with miR-155 targeting agents might improve the outcome of TSA-based therapies [123]. In lung cancer cells, the levels of the tumor suppressors miR-15a, miR-16-1, and miR-373 were increased after treatment with TSA [124,125]. MiR-15a and miR-16-1 were also induced by TSA in mantle cell lymphoma cells [126]. In liver cancer cells, miR-129, miR-182-3p and miR-449 were upregulated by TSA, as well as miR-129-5p in thyroid cancer cells and miR-375 in tongue cancer cells [127–129]. In addition, the overexpression of the microRNAs miR-30d, miR-181a and miR-199a-5p enhanced the anticancer activity of TSA via suppression of the ER-chaperone GRP78 (glucose-regulated protein) [130]. Colon cancer cells treated with TSA showed increased levels of the tumor suppressor miR-449a/b leading to inhibition of Fra-1 and of tumor cell growth and migration [131]. In combination with the antimetabolite 5-aza-CdR, TSA increased the expression of miR-29b, miR-30b and miR-31 [132]. In gastric cancer cells, TSA plus 5-aza-2'-deoxycytidine increased the expression of the tumor suppressor miR-10b leading to tumor growth inhibition, reduced migration and invasion, and enhanced apoptosis induction [133]. Similarly, the tumor suppressor miR-219-2-3p was induced by TSA and 5-aza-2'-deoxycytidine in gastric cancer cells associated with suppression of p-ERK1/2 [134]. In HCC cells, TSA plus 5-aza-2'-deoxycytidine increased the expression of miR-362-3p leading to suppression of the cell cycle regulator Tob2 and to reduced tumor cell proliferation and suppressed anchorage-independent growth [135]. In addition, combination of TSA with 5-azaC enhanced tumor suppressor miR-1-1 expression while combination of TSA with the DNMT inhibitor zebularine induced miR-26b and let-7a expression [136–138].

Polyunsaturated fatty acids (PUFAs), in particular, n-3 PUFAs such as docosahexaenoic acid (DHA, Fig. 7) and eicosapentaenoic acid (EPA) feature significant constituents of fish oil and revealed distinct tumor suppressive effects, for instance, enhanced protection against colon tumorigenesis [139–142]. Rats fed with fish oil rich in n-3 PUFAs revealed reduced carcinogenic effects of azoxymethane (AOM) in rat colons by upregulation of let-7d, miR-15b, miR-107, miR-191, and miR-324-5p [143]. PUFAs such as DHA and γ -linolenic acid induced apoptosis in glioma cells by specific downregulation of miR-143 while miR-20b was upregulated [144]. DHA distinctly increased the levels of tumor suppressing (let-7a) and anti-angiogenic miRNAs (miR-21, miR-23b, miR-27b, miR-320b) in the exosomes of breast cancer cells (MCF-7, MDA-MB-231) while non-malignant breast cells exhibited no differences [145]. Increased expression of miR-23b and miR-320b downregulated the expression of pro-angiogenic targets (PLAU, AMOTL1, NRP1, ETS2) and contributed to the anti-angiogenic activity of DHA [145]. Another study reported the suppression of the oncomir miR-21 by DHA in breast cancer cells (MCF-7, MDA-MB-231) leading to increased expression of PTEN and reduction of CSF-1 [146]. Mice injected with HT-29 colon cancer showed reduced tumor growth when fed with a walnut diet leading to increased levels of n-3 PUFAs such as DHA and EPA in the mice [147]. The anticancer effects of the walnut diet were mediated by suppression of miR-467c, miR-1903, and miR-3068, and overexpression of miR-297* [147]. A list of miRNAs regulated by aliphatic carboxylic acids is given in Table 6.

2.4. Water-soluble vitamins

Folic acid (FA, vitamin B9) is a natural vitamin occurring in grains, fruits and vegetables and plays an important role concerning DNA biosynthesis, DNA repair and DNA methylation (Fig. 8) [148]. FA also modulated miRNAs involved in the development of different cancer types. Rats fed with a folate-deficient diet produced HCC after one year associated with upregulation of let-7a, miR-21, miR-23, miR-130, miR-190, and miR-17-92 as well as suppression of miR-122 in the developed hepatomas [149]. FA consumption was accompanied by upregulation of miR-122 leading to efficient blocking of liver tumorigenesis [149,150]. In addition, increased expression of miR-222 was observed from lymphoblastoid cells devoid of FA supplement [151]. FA was also applied for certain “theranostic” purposes involving miRNAs since FA receptors are often overexpressed on the cell surface of cancer cells. A nanoprobe consisting of a gold nanoparticle modified with a fluorescein isothiocyanate (FITC)-labelled molecular beacon (MB that

Table 6
Regulation of microRNAs by natural aliphatic carboxylic acids.

Compounds	Tumor suppressors (up-regulated)	Oncogenes (down-regulated)
NaB	miR-15a [112], miR-16-1 [112], miR-31 [115], miR-95 [110], miR-96 [110], miR-101 [113], miR-125a-5p [114], miR-143 [113], miR-145 [113], miR-183 [110], miR-184 [110], miR-202 [110], miR-487b [110], miR-194 [110], miR-215 [110], miR-300 [110], miR-320b [110], miR-381 [110], miR-424 [110], miR-492 [110], miR-583 [110], miR-602 [110], miR-637 [110], miR-874 [110], miR-1908 [110]	miR-17-92 cluster [110], miR-106a-363 cluster [110], miR-106b-25 cluster [110], let-7b-3p [110], miR-7 [110], miR-34a [110], miR-106b [111], miR-135a [110], miR-196b [110], miR-221 [110], miR-222-5p [110], miR-886 [110]
TSA	miR-1 [123], miR-7 [121], miR-15a [124-126], miR-16-1 [124-126], miR-22 [123], miR-125a-5p [122], miR-129 [127,128], miR-139 [123], miR-143 [123], miR-144 [123], miR-153 [123], miR-182-3p [127], miR-191* [123], miR-194 [123], miR-202* [123], miR-215 [123], miR-335 [123], miR-373 [124,125], miR-375 [129], miR-449a/b [127,131], miR-486 [123], miR-559 [123]	miR-106b-93-25 cluster [120], miR-500 [123], miR-645 [123]
TSA + antimetabolites	miR-1-1 [136,137], miR-10b [133], miR-29b [132], miR-30b [132], miR-31 [132], miR-219-2-3p [134], miR-362-3p [135]	–
TSA + zebularine n-3 PUFAs	let-7a [138], miR-26b [138] let-7a [145], let-7d [143], miR-15b [143], miR-20b [144], miR-21 (anti-angiogenic) [145], miR-23b [145], miR-27b [145], miR-107 [143], miR-191 [143], miR-297* [147], miR-324-5p [143], miR-320b [145]	– miR-21 [146], miR-143 [144], miR-467c [147], miR-1903 [147], miR-3068 [147]

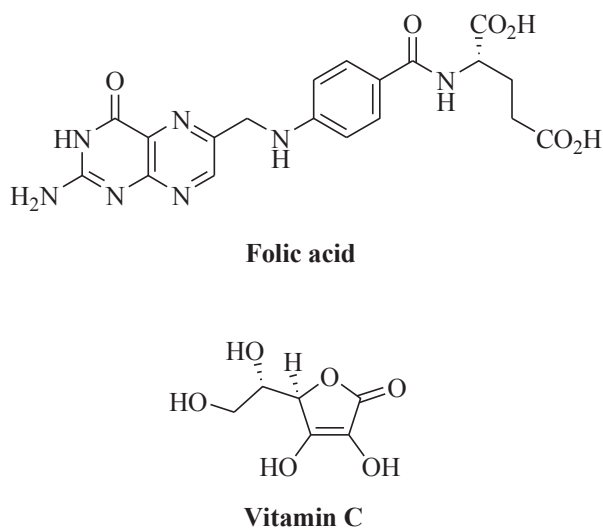


Fig. 8. Structures of folic acid and vitamin C.

binds to miR-21) and PEGylated FA was prepared which docked to cancer cells via the FA receptor [152]. Inside the cell, miR-21 bound to the MBs of the nanoprobe induced a fluorescence signal which determined the miR-21 level within the cancer cells. Subsequent irradiation with NIR (near infrared) light caused apoptosis via photothermal effects of the gold nanoparticle which enhanced the fluorescence signal since remaining unbound MBs were unwinded at higher temperatures [152]. Similarly, gold nanocages modified

with PEGylated FA were able to bind and to deliver anti-miR-181b molecules into HCC cells and the combined effects of the nanoprobes comprising photothermal therapy and miR-181b suppression distinctly reduced tumor growth both *in vitro* and *in vivo* after NIR irradiation [153].

Vitamin C (ascorbic acid) features a natural tetronic acid with potent antioxidant properties and occurs in many easily available fruits and vegetables (Fig. 8). Already Cameron and Campbell had discovered the potent anticancer properties of vitamin C and an initial clinical trial with terminal cancer patients who received a combination of vitamin C infusions (10 g/day, *i.v.* for 10 days) and oral vitamin C (10 g/day, 10 days) exhibited distinctly longer medium survival in the vitamin C group (210 days) when compared with untreated patients (50 days) [154,155]. A clinical study of the Mayo Clinic used only oral vitamin C and, thus, could not reproduce the promising results of Cameron and coworkers which underlines the high importance of intravenous application of vitamin C in order to reach sufficient blood plasma concentrations of vitamin C (up to 5.5 mmol/L after 10 g vitamin C, *i.v.*; up to 13.5 mmol/L after 50 g vitamin C, *i.v.*) [156–158]. Several newer cancer case studies and trials that applied high-dose vitamin C infusions reported of significant tumor remission and reduced side-effects when combined with chemotherapeutic agents (e.g., paclitaxel) [159–164]. A phase I clinical trial of the combination of vitamin C and gemcitabine in metastatic pancreatic cancer patients (PACMAN study) revealed a mean survival time of 13 months, which was more than twice of the mean survival time of patients treated only with gemcitabine (5.65 months) [164,165]. The mode of action of vitamin C comprises the production of toxic H₂O₂ molecules that kill the cancer cells in a selective way [158,166]. Resistance to vitamin C was mediated by hypoxic conditions and HIF-1 α

Table 7
Regulation of microRNAs by water-soluble vitamins.

Compounds	Tumor suppressors (up-regulated)	Oncogenes (down-regulated)
Folic acid	miR-122 [149,150]	let-7a [149], miR-21 [149], miR-23 [149], miR-130 [149], miR-190 [149], miR-17-92 [149], miR-222 [151]
Vitamin C	miR-125b-2 [170], miR-134 [170], miR-135a [170], miR-345 [170], miR-375 [170], miR-422a [170], miR-490-5p [170], miR-516a-3p [170], miR-596 [170], miR-630 [170], miR-663 [170], miR-708 [170], miR-1228 [170], miR-1915 [170]	miR-93 [168], miR-153 [169]

expression [167]. The effects of ascorbic acid on the expression of microRNAs were investigated as well. In breast tissues, vitamin C inhibited carcinogenesis via suppression of oncogenic miR-93 associated with increased NRF2 (nuclear factor erythroid 2-related factor 2) expression [168]. Similarly, in a more recent study vitamin C inhibited breast carcinogenesis by suppression of oncogenic miR-153 leading likewise to upregulation of NRF2 [169]. In melanoma cells, vitamin C increased the expression of 14 tumor suppressing and EMT reversing miRNAs (miR-596, miR-630, miR-422a, miR-490-5p, miR-375, miR-708, miR-345, miR-125b-2, miR-516a-3p, miR-135a, miR-1228, miR-1915, miR-134, miR-663) [170]. The expression of miR-596, miR-630, miR-490, miR-375 and miR-708 prolonged the overall survival of cancer patients when compared with patient groups exhibiting only low expression of these miRNAs [170]. A list of miRNAs regulated by water-soluble vitamins is given in Table 7.

3. Conclusions

The expression of microRNAs involved in cancer-related processes such as cell death, cell differentiation and proliferation, angiogenesis and metastasis formation was modulated by several natural and dietary compounds of known anticancer activity. The effects of natural drugs selected from the classes of alkaloids, organosulfur compounds, aliphatic carboxylic acids and water-soluble vitamins on microRNAs contribute to their sound anticancer activities. Low toxicity and reduced side-effects were already observed from animal studies and clinical trials for several of these natural compounds (e.g., DIM, vitamin C, etc.) that add significantly to conventional cancer therapies in consequence. In addition, the activity of approved alkaloid anticancer agents such as Vinca alkaloids and camptothecin and its derivatives was regulated and strongly influenced by various tumor suppressor and oncogenic miRNAs. In order to improve currently applied anticancer therapies, a thorough knowledge of the regulation of relevant miRNAs by small molecule natural products and dietary factors is crucial. The therapeutic modulation of miRNAs harbors outstanding prospects for anticancer patients such as better prognosis, improved quality of life, and prevention of drug resistance.

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