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REVIEW – CANCER RESEARCH

The role of dietary phytochemicals in the carcinogenesis via the modulation of miRNA expression

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Abstract

Purpose Phytochemicals are naturally occurring plant-derived compounds and some of them have the potential to serve as anticancer drugs. Based on recent evidence, aberrantly regulated expression of microRNAs (miRNAs) is closely associated with malignancy. MicroRNAs are characterized as small non-coding RNAs functioning as posttranscriptional regulators of gene expression. Accordingly, miRNAs regulate various target genes, some of which are involved in the process of carcinogenesis.

Results This comprehensive review emphasizes the anticancer potential of phytochemicals, either isolated or in combination, mediated by miRNAs. The ability to modulate the expression of miRNAs demonstrates their importance as regulators of tumorigenesis. Phytochemicals as anticancer agents targeting miRNAs are widely studied in preclinical in vitro and in vivo research. Unfortunately, their anticancer efficacy in targeting miRNAs is less investigated in clinical research.

Conclusions Significant anticancer properties of phytochemicals as regulators of miRNA expression have been proven, but more studies investigating their clinical relevance are needed.

Keywords microRNAs · Phytochemicals · Plant-derived food · Cancer · Carcinogenesis

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Introduction

Cancer is one of the major health problems worldwide (Ghoncheh et al.2016; Patafio et al. 2016). Malignant diseases represent heterogeneous tumor types in its ethology and pathological properties (Tao et al. 2015). Genetic and epigenetic alterations are particularly important for the formation and development of cancer (Uramova et al. 2018; Golubnitschaja et al. 2016); hence epigenetic changes represent important mechanisms in tumor initiation and progression (Pasculli et al. 2018). In addition to the standard epigenetic mechanisms (DNA methylation, histone modification), non-coding RNAs, especially miRNAs and long non-coding RNAs, are important epigenetic modifiers in the regulation of gene expression (Peschansky and Wahlestedt 2014). Some bioactive compounds naturally occurring in plants, known as phytochemicals, and other essential nutrients can promote human cancer by upregulating expression of various oncogenic miRNAs and thus influence the cellular processes including increased proliferation or drug resistance (Rigalli et al. 2016; Sayeed et al. 2017; Ross and Davis 2014; Bespalov et al. 2018). Otherwise, phytochemicals can suppress tumor initiation, promotion, and metastasis via epigenetic regulation of miRNA expression. Phytochemicals may also improve the sensitivity of cancer cells to standard chemotherapy via modulation of miRNA expression, thus, representing a potentially interesting target in cancer therapy (Kapinova et al. 2018; Srivastava et al. 2015).

Aim of the study

The review focuses on anticancer effects of phytochemicals mediated via regulation of epigenetic mechanisms targeting the expression of miRNAs in cancer cells. The function, biogenesis, and participation of miRNAs in the processes of carcinogenesis are discussed. Based on current research, some phytochemicals are associated with significant anticancer efficacy. The aim of our review was to bring together the experimental (in vitro/in vivo) and clinical studies focusing on plant-derived compounds (isolated and/or mixtures) and their modulating potential in regulation of miRNAs expression in cancer cells.

Source of data

Data were recovered from the literature published in the English by use of "microRNA" and "cancer" or "phytochemicals" or "functional foods" or "vegetables" or "fruits" or "spices" or "grains" as a keyword in the PubMed bibliographic database. The database was accessed between January 2019 and February 2019 with the focus placed on the most recent scientific papers from the years 2014 to 2018.

MicroRNAs (miRNAs)

MicroRNAs are approximately 22nt in length small, non-protein coding RNAs (ncRNAs) that are associated with several biological processes of cells (Weiss and Ito 2017). Mechanisms of miRNA modulation include regulation of gene expression at the post-transcriptional level by binding to the 3′ untranslated region of primary transcript mRNA. The complementarity of miRNA to mRNA through base-pairing leads to the cleavage of the primary transcript, inducement of mRNA degradation and translational repression (Dong et al. 2016; O'Brien et al. 2018; Oliveto et al. 2017; van Schooneveld et al. 2015). The detailed description of miRNAs' biogenesis, which is mediated either via canonical or non-canonical pathway, is demonstrated in Fig. 1. Actually, over 2000 miRNAs are identified in human genome while the small non-coding RNAs can regulate expression of protein-coding genes (Catalanotto et al. 2016; Gurtan and Sharp 2013; Kim et al. 2018). Currently, researchers focus on miRNAs as potential diagnostic or prognostic markers and predictors of the success of cancer therapy (Chen et al. 2015; Liu et al. 2016; Qadir and Faheem 2017; Zubor et al. 2018).

The events leading to alterations of miRNA expression

The alterations of miRNAs represent cascade in both transcriptional as well as post-transcriptional regulation mechanisms. MicroRNAs' expression at transcriptional level is associated with hypermethylation of the promoter regions and directly connected to the modulation of gene expression, whilst post-transcriptional regulation demonstrates differences in miRNA processing (Treiber et al. 2018). MicroRNA expression is tightly controlled by epigenetic regulation, including gene silencing via methylation, respectively, hydroxymethylation of DNA enhancing transcriptional or post-transcriptional modifications of histones, especially acetylation and methylation (Morales et al. 2017; Pan et al. 2016). Moreover, endogenous factors, such as hormones and cytokines together with exogenous factors (e.g. xenobiotics) play significant role in the regulation of miRNA expression (Gulyaeva and Kushlinskiy 2016; Catalanotto et al. 2016). Importantly, recent evidence has shown that dysregulation of miRNA is related to the single nucleotide polymorphism leading to difference in maturation of this small non-coding RNA (Wilk and Braun 2018). Furthermore, posttranscriptional cross-regulation between essential components of microprocessor machinery Drosha and DGCR8, in which their imbalance is associated with defects in miRNA maturation, is another regulation process involved in miRNA dysregulation (Herbert et al. 2016). In addition, p68 and

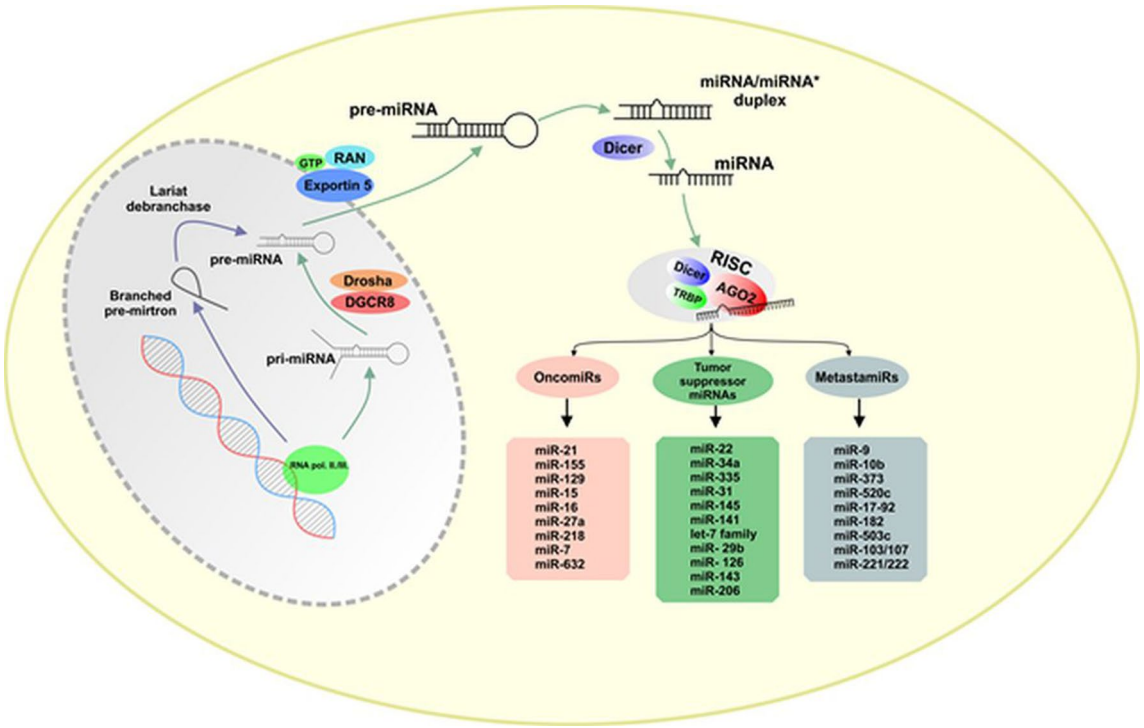

Fig. 1 Biogenesis of miRNA via canonical and non-canonical pathways (Abba et al. 2017; Feng and Tsao 2016; Jiang et al. 2010; Kim et al. 2018; Kurozumi et al. 2017; Lin and Gregory 2015; Macfarlane and Murphy 2010; Mehrgou and Akouchekian 2017; Nakanishi 2016; O'Brien et al. 2018; Rupaimoole and Slack 2017; Setijono et al. 2018; Shah et al. 2016; Takahashi et al. 2015; Zubor et al. 2018). In canonical biogenesis, miRNA is transcribed by RNA polymerase II/III from miRNA gene to primary miRNA (pri-miRNA) which is processed by Drosha and DiGeorge Syndrome Critical Region 8 (DGCR8) to ~ 70 nt precursor-miRNA (pre-miRNA). Then, pre-miRNA is exported to cytoplasm via nucleocytoplasmatic transporter Exportin5 (Exp5) and RanGTP-dependent manner. In cytoplasm pre-miRNA undergoes cleavage by Dicer to single-strand miRNA. Maturated miRNA (~ 22 nt) together with Dicer, TAR RNA binding protein (TRBP), and Argonaute protein (AGO2) forms RNA-induced silencing complex (RISC). Non-canonical pathway of miRNA biogenesis is mediated via miRNA encoded in regions of intron of protein coding genes while a mirtron structure is generated. Then, lariat debranchase continues the biogenesis by forming the pre-miRNA. MiRNA together with RISC has an effector function and can act as oncomiRs and metastamiRs in cancer progression and invasion. Additionally, it might play a vital role as a tumor suppressor miRNA in suppression of carcinogenesis via complementary to their targets mRNA

p72 helicases are well-characterized components of nuclear microprocessor complex of the cell (Drosha, DGCR8), while their connection to spliceosome induce effector action in splicing of pri-miRNA into pre-miRNA. Changes in *p68/p72* gene expressions, e.g. in pathologically altered cells leads to the disequilibrium between level of pri-miRNA and pre-miRNA, whereas in normal cells their levels are equal (Remenyi et al. 2016). Similarly, other groups of intracellular proteins, known as SMAD, are related to the regulation of miRNA expression via signal transduction of TGF-β pathway (Blahna and Hata 2012). Currently, several studies have shown that relationship between estrogen signaling and regulation of miRNAs via interaction with Drosha leads to the rapid dissociation of the microprocessor complex from pri-miRNA during maturation (Klinge 2015; Katchy and Williams 2014). Additionally, RNA-binding protein (LIN28) is an important regulator of let-7, the most abundant miRNA family with high expression rates in most tissues, excluding embryonic stem cells. The consequence of an interaction between RNA-binding protein and the single-stranded loop area of precursor let-7 is an increased level of LIN28 that reduces let-7 via blockage of the maturation (Ustianenko et al. 2018). Interestingly, divergence in miRNA levels can be regulated by competing endogenous RNAs (ceRNA). There are several elements which can act as ceRNAs, including long non-coding RNAs, protein coding RNAs, or pseudogenes that share miRNA recognition elements (MREs) and thereby regulate their expression (Kartha and Subramanian 2014; Chiu et al. 2018).

MicroRNAs in cancer progression

MicroRNAs regulate gene expression via suppression and degradation of primary transcripts of genes. In the past decade, global profiling of tissues from patients compared to healthy controls identified several dysregulated miRNAs in various human cancers (Hamam et al. 2016). Aberrant regulation of miRNA expression has fundamental effects

on cancer initiation, progression, drug resistance, and is also associated with metastases. Moreover, miRNAs are implicated in multipotent cells exhibiting stem-like properties known as cancer stem cells (CSCs) (Gandhi et al. 2014). As shown in Fig. 1, miRNAs can act as tumor suppressors (tumor-suppressors miRNAs) (miR-335, -31, -145, -141, -34a, -22, -let-7 family, -29b, -126, -143, -206), oncogenes (oncomiRs) (miR-15, -16, -21, -155, -129, -27a, -218, -7, -632) or play vital role in the metastatic progression (metastamiRs) (miR-9, -10b, 373, -520c, miR-17–92 cluster, -182, -503c, -103/107, -221/222) in various cancer types (Abba et al. 2017; Feng and Tsao 2016; Jiang et al. 2010; Kim et al. 2018; Kurozumi et al. 2017; Setijono et al. 2018; Shah et al. 2016). Upregulation of oncogenic miRNAs leads to the inhibition and degradation of products of tumor suppressor genes that code proteins regulating growth of cells. On the contrary, tumor-suppressor miRNAs are associated with inhibition of primary transcripts of oncogenes that promote cell proliferation. Several metastamiRs play an important role in the regulation of metastases through various mechanisms, such as migration, colonization, metastasis or epithelial-mesenchymal transition (EMT) (McGuire et al. 2015; Lopez-Camarillo et al. 2012). Finally, alterations of miRNA expression affect intracellular processes involved in progression of carcinogenesis; moreover, different miRNA expression profiles can define various subtypes of tumors (Dahiya et al. 2008; Chan and Wang 2015; Li et al. 2015b; Tsai et al. 2018; Zhang et al. 2016).

Mechanisms of miRNAs regulating carcinogenesis

As mentioned above, miRNAs function as important regulators of carcinogenesis (Guan et al. 2017; Lima et al. 2011). Detailed overview of pro-oncogenic processes modulated via impaired expression of miRNAs is demonstrated in Fig. 2.

Cancer cells are characterized by enhanced proliferation and apoptosis avoidance. Abnormal proliferation of cancer cells is mediated via alterations in cell cycle-related proteins or signaling pathways regulating cell growth (Feitelson et al. 2015). Importantly, proliferation of cancer cells was found to be enhanced in response to the deregulated expression of miR-140-5p, miR-320, miR-126, miR-93, and miR-7 in ovarian (Lan et al. 2015), breast (Bai et al. 2017; Wang et al. 2015), gastric (Guan et al. 2017) or other cancer types (Webster et al. 2009). Moreover, alterations in expression of miR-200c, miR-221, and miR-222 were also associated with enhanced proliferation of gastric cancer (Wang et al. 2016) and glioblastoma cells (le Sage et al. 2007).

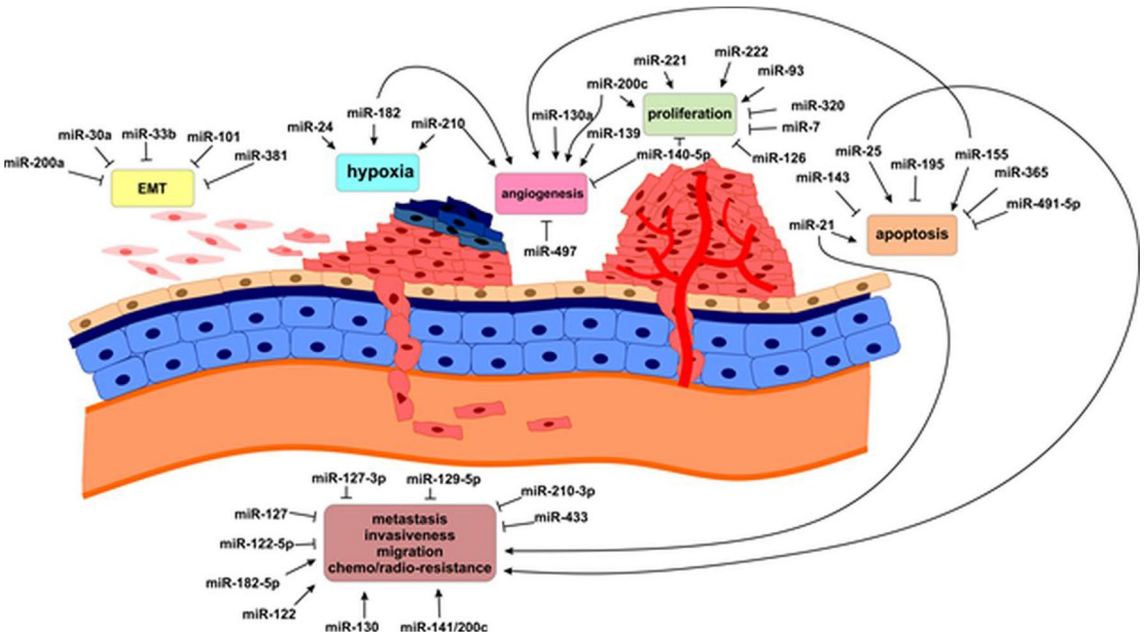

Fig. 2 MicroRNAs regulating proliferation, apoptosis, EMT, invasiveness, migration, metastases, angiogenesis, and adaptation to hypoxia of cancer cells (Bahena-Ocampo et al. 2016; Bai et al. 2017; Cheng et al. 2012; Choi et al. 2016; Cong et al. 2013; Du et al. 2015; Duan et al. 2016; Fan et al. 2018; Gong et al. 2015; Gu et al. 2018; Guan et al. 2017; Guo et al. 2012, 2013, 2014; Hatley et al. 2010; Jiang et al. 2014; Kong et al. 2014; Korpal et al. 2008; Kumarswamy et al. 2012; Lan et al. 2015; Li et al. 2014b, 2015a, c, 2017a, c; Liu et al. 2012, 2013, 2014; Lu et al. 2017; Martin del Campo et al. 2015; Pang et al. 2017; Qu et al. 2015; Razumilava et al. 2012; Roscigno et al. 2017; le Sage et al. 2007; Shi et al. 2016; Song et al. 2017; Wang et al. 2014a, 2015, 2016, Wang et al. 2018a; Webster et al. 2009; Wu et al. 2017; Xu et al. 2017, 2018; Xue et al. 2016; Yang et al. 2016, 2017, 2018; Zhan et al. 2016; Zhu et al. 2015)

Apoptosis is defined as a programmed cell death in which variety of gene products are involved. Both intrinsic and extrinsic apoptotic pathways contribute to the activation of caspases, effectors or initiators of programmed cell death. Importantly, defects in apoptosis lead to the loss of cell growth control and thus cause malignancy (Li et al. 2012). Deregulated expression of miR-195, miR-143, miR-365, miR-222, and miR-491-5p was associated with apoptosis avoidance in various malignancies including breast (Zhu et al. 2015), cervical (Liu et al. 2012), hepatocellular (Li et al. 2017c), pancreatic (Guo et al. 2012), and oral squamous cell carcinoma (Jiang et al. 2014). Furthermore, miR-21 and miR-155 were found to target genes involved in apoptosis in diffuse large B cell lymphoma (Song et al. 2017), gastric adenocarcinoma (Gu et al. 2018), colorectal cancer (Wu et al. 2017), and lung tumorigenesis (Hatley et al. 2010; Xue et al. 2016). Interestingly, miR-10b promoted renewal of breast cancer stem cells (Bahena-Ocampo et al. 2016) and miR-25 protected cholangiocarcinoma cell lines from TRAIL-induced apoptosis (Razumilava et al. 2012). Moreover, miR-34a family, as the most prevalent p53-induced miRNAs (Rokavec et al. 2014), influenced the cancer cell death resistance via regulation of p53 pathway in various cancers (Koo and Kwon 2018).

EMT is characterized as a loss of epithelial and acquisition of mesenchymal markers. Importantly, altered expression of several miRNA target genes involved in EMT, which is an important process allowing cancer cells to gain motility and invasiveness, is associated with cancer progression and formation of metastasis (Rhodes et al. 2015; Chan and Wang, 2015; Guo et al. 2014). Importantly, MiR-200 family is a key regulator of EMT (Korpal et al. 2008) as was demonstrated in gastric adenocarcinoma (Cong et al. 2013). Interestingly, miR-381 promoted expression of SOX4, a master mediator of EMT in gastric carcinoma (Pang et al. 2017) and miR-101 regulated EMT in ovarian carcinoma (Guo et al. 2014). Moreover, abnormal expression of miR-30a was associated with EMT in hepatocellular carcinoma (Liu et al. 2014), non-small cell lung carcinoma (Kumarswamy et al. 2012), and breast cancer (Cheng et al. 2012). Altered expression of miR-33b promoted also EMT phenotype of lung adenocarcinoma (Qu et al. 2015). As mentioned above, changes in expression of miRNAs may lead to promotion of invasiveness, migration, and metastasis (Chan and Wang 2015). Significantly, miR-21 enhanced invasiveness in melanoma (Martin del Campo et al. 2015) and promoted growth, metastasis, and chemo/radio-resistance in non-small cell lung carcinoma cells (Liu et al. 2013). Moreover, altered expression of miR-141/200c cluster promoted migration and invasiveness of triple-negative breast cancer (Choi et al. 2016). Furthermore, several other miRNAs including miR-548j, miR-25, miR-210-3p, miR-122, miR-122-5p, miR-182-5p, miR-129-5p, miR-433, miR-127, miR-127-3p, and miR-130 promoted invasiveness, migration or metastasis in breast (Zhan et al. 2016), gastric (Duan et al. 2016; Gong et al. 2015; Guo et al. 2013; Li et al. 2017a; Xu et al. 2018) or bladder cancer cells (Yang et al. 2017), clear-cell renal cell carcinoma (Fan et al. 2018), osteosarcoma (Wang et al. 2018a), and in glioblastoma cells (Xu et al. 2017).

Multiple cellular and molecular mechanisms are associated with cells responding to changes in oxygen tension. Hypoxia is characterized as a reduction of the normal level of tissue oxygen tension which is related to several diseases including cancer (Bandara et al. 2017). Hypoxia is followed by alterations in DNA transcription in conjunction with hypoxia-inducible factors (HIFs) which are considered to be main components of hypoxia signaling pathways. Overall, more than a thousand target genes are regulated by HIFs (Ke et al. 2017). Therefore, hypoxia-regulated genes are related with numerous major processes of carcinogenesis including angiogenesis, apoptosis, proliferation, and metastasis (Winther et al. 2016). Importantly, the HIF subunit, HIF-1α, regulates adaptation of cells to hypoxic condition through association with various miRNAs. MiR-210 is the most responsive miRNAs regulated by hypoxia (Dang and Myers 2015; Shen et al. 2013). Moreover, miR-24 increased adaptation to hypoxic conditions of breast cancer stem cells (Roscigno et al. 2017) and miR-182 showed similar effects in prostate cancer cells (Li et al. 2015c). Hypoxia-based upregulation of miR-210 promoted growth in ovarian cancer (Li et al. 2014b). Additionally, angiogenesis is defined as a formation of new blood vessels from pre-existing ones (Wang et al. 2018c) playing an important role during embryogenesis and tissue homeostasis in adults. However, the neovascularization is also tightly associated with carcinogenesis. Importantly, interaction of miRNAs and their target genes is involved in the regulation of angiogenesis in cancer cells (Lu et al. 2017). MiR-210, as the master hypoxia-induced miRNA, promoted angiogenesis in hepatocellular carcinoma (Yang et al. 2016) and hypoxia-regulated expression of miR-182 elevated angiogenesis and thus adaptation of hepatocellular cancer cells under hypoxic conditions (Du et al. 2015). Moreover, aberrantly expressed miR-140-5p, miR-155, miR-449a, miR-139, and miR-200c promoted angiogenesis in breast (Kong et al. 2014; Lu et al. 2017; Shi et al. 2016) and pancreatic cancer (Li et al. 2015a). Exosome-derived miR-130s of gastric cancer cells delivered into vascular endothelial cells also promoted angiogenesis (Yang et al. 2018). Accordingly, altered expression of miRNAs can change the expression of gene products with anti- or pro-oncogenic effects (Tan et al. 2017). Table 1 shows more detailed overview of processes associated with malignancy which are modulated via changes in expression of selected miRNAs.

Table 1 Detailed overview of selected miRNAs involved in cancer regulation

Mechanism of miRNAs regulation of cancer	MicroRNAs	Target pathway/gene product	References
↑ Proliferation	↑ miR-93; ↑ miR-200c; ↑ miR-221; ↑ miR-222; ↓ miR-7; ↓ miR-126; ↓ miR-140-5p; ↓ miR-320	TIMP2, $P27^{Kip1}$, SOX4, EGFR, ADAM9, PDGFRA	Bai et al. (2017), Guan et al. (2017), Lan et al. (2015), le Sage et al. (2007), Wang et al. (2015, 2016), Webster et al. (2009)
↓ Apoptosis	↑ miR-10b; ↑ miR-21; ↑ miR-25; ↑ miR-155; ↑ miR-222; ↓ miR-143; ↓ miR-195; ↓ miR-365; ↓ miR-491-5p	Bcl-2, Bcl-xL, PUMA, PTEN, DR4, TP53, SOCS1, SOCS6, AKT, Ras/MEK/ERK	Bahena-Ocampo et al. (2016), Gu et al. (2018), Guo et al. (2012), Hatley et al. (2010), Jiang et al. (2014), Li et al. (2017c), Liu et al. (2012), Razumilava et al. (2012), Song et al. (2017), Wu et al. (2017), Xue et al. (2016), Zhu et al. (2015)
↑ EMT	↓ miR-30a; ↓ miR-33b; ↓ miR-101; ↓ miR-381; ↓ miR-200 family (miR-200a)	ZEB1/ZEB2, vimentin, Wnt/β-catenin/ZEB1, SOX4, Snai1	Cheng et al. (2012), Cong et al. (2013), Guo et al. (2014), Korpal et al. (2008), Kumarswamy et al. (2012), Liu et al. (2014), Pang et al. (2017), Qu et al. (2015
↑ Invasiveness ↑ Migration ↑ Metastases ↑ Chemo/radio-resistance	↑ miR-21; ↑ miR-25; ↑ miR-122; ↑ miR-130; ↑ miR-141/200c; ↑ miR-182-5p; ↑ miR-548j; ↓ miR-122-5p; ↓ miR-127; ↓ miR-127-3p; ↓ miR-129-5p; ↓ miR-210-3p; ↓ miR-433	TIMP3, PTEN, FBXW7, KRAS, MAPK, ITGA6, TGFβR2, VEGF-A, DUSP4, FGFRL1, RAB27A, FNDC3B, Dicer, TNS1	Choi et al. (2016), Duan et al. (2016), Fan et al. (2018), Gong et al. (2015), Guo et al. (2013), Li et al. (2017a), Liu et al. (2013), Martin del Campo et al. (2015), Wang et al. (2018a), Xu et al. (2017, 2018), Yang et al. (2017), Zhan et al. (2016
↑ Adaptation to hypoxia	↑ miR-24; ↑ miR-182; ↑ miR-210	FIH1, HIF-1α, PHD2, PTPN1	Li et al. (2014b, 2015c), Roscigno et al. (2017)
↑ Angiogenesis	↑ miR-130a; ↑ miR-139; ↑ miR-155; ↑ miR-182; ↑ miR-200c; ↑ miR-210; ↑ miR-449a; ↓ miR-140-5; ↓ miR-497	VEGF-A, VEGFR2, RASA1, c-MYB, VHL, FGFRL1, CRIP2, HIF-1α	Du et al. (2015), Kong et al. (2014), Li et al. (2015a), Lu et al. (2017), Shi et al. (2016), Wang et al. (2014a), Yang et al. (2016, 2018)

Explanatory notes: ↑ increase, ↓ decrease

ADAM9 A disintegrin and metalloproteases 9, *AKT* protein kinase B, *Bcl-xL* B-cell lymphoma-extra large, *Bcl-2* B-cell lymphoma, *CRIP2* cysteine-rich protein 2, *DR4* Death Receptor-4, *DUSP4* Dual Specificity Phosphatase 4, *FBXW7* F-box and WD-40 domain protein 7, *FGFRL1* fibroblast growth factor receptor-like 1, *FIH1* factor-inhibiting HIF hydroxylase 1, *FNDC3B* Fibronectin Type III Domain Containing 3B, *HIF1α* hypoxia-inducible factor 1α, *ITGA6* integrin subunit-α 6, *KRAS* Ki-ras2 Kirsten rat sarcoma viral oncogene homolog, *MAPK* mitogen-activated protein kinase 4, *PDGFRA* platelet-derived growth factor receptor A, *PHD2* hypoxia-inducible factor prolyl hydroxylase 2, *PTEN* phosphatase and tensin homolog, *PTPN1* tyrosine-protein phosphatase non-receptor type 1, *PUMA* the p53 upregulated modulator of apoptosis, $p27^{Kip1}$ cyclin-dependent kinase inhibitor 1B, *RAB27A* Ras-related protein Rab-27A, *RASA1* RAS p21 protein activator 1, *SNAI1* snail family zinc finger 1, *SOCS1* suppressor of cytokine signaling 1, *SOCS6* suppressor of cytokine signaling 6, *SOX4* the SRY-box 4, *TGFβR2* the transforming growth factor beta receptor-2, *TIMP2* tissue inhibitor of metalloproteinase 2, *TIMP3* tissue inhibitor of metalloproteinases 3, *TNS1* Tensin 1, *TP53* tumor protein p53, *VEGF* vascular endothelial growth factor, *VHL* von Hippel–Lindau tumor suppressor, *ZEB1* Zinc finger E-box-binding homeobox 1, *ZEB2* Zinc finger E-box-binding homeobox 2

Natural compounds

Phytochemicals are characterized as bioactive compounds present in plant-derived food such as vegetables, fruits, grains, beans or others, having antioxidant, antineoplastic, and antiangiogenic efficacy in various cancer types (Abbasi et al. 2018; Kubatka et al. 2017; Chiou et al. 2018). Since the first identification of miRNAs in 1993, researchers have studied their significant role in molecular mechanisms including initiation, promotion, and progression of tumorigenesis (Abotaleb et al. 2018; Ladomery et al. 2011; Varghese et al. 2018). Up to now, number of studies have been focusing on bioactive compounds such as isolated agents (curcumin, resveratrol, sulforaphane, epigallocatechin-3-gallate, genistein, ellagic acid, indole-3 carbinol) or a mixture of agents from plant-derived foods which have been tested as modulators of expression of number oncogenic and tumor suppressive miRNAs (de la Parra et al. 2016; Hargraves et al. 2015; Kapinova et al. 2018; Sayeed et al. 2017; Bespalov et al. 2017).

Preclinical research

Epigallocatechin-3-gallate (EGCG) is the most efficient anticancer compound of green tea. The anticancer effects of EGCG are demonstrated in various tumor cell lines and animal models through modulation of cell cycle arrest, apoptosis, and angiogenesis including regulation of miRNAs expression. Significantly, EGCG induced alterations of 14 miRNAs in CNE2 cells of human nasopharyngeal carcinoma in a dose-dependent manner (20 µmol/L, 40 µmol/L), with the regulation of MAPK or Wnt signaling pathway as the potential anticancer mechanism (Li et al. 2017a; Yuan 2013). EGCG upregulated also expression of miRNA-let-7b and inhibited tumor growth by activating 67 kDa laminin receptor signaling in B16 melanoma cells (Yamada et al. 2016). Moreover, increase in expression of miR-210 in response to HIF-1α binding was demonstrated after administration of EGCG in an in vivo mouse model of lung cancer. Importantly, the stabilization of HIF-1α by EGCG was associated with reduced cell proliferation and anchorage-independent growth (Zhou et al. 2014).

Resveratrol (*trans*-3,4′,5-trihydroxystilbene) is a natural compound present in plants such as grapevines, pines, peanuts, berries or grapes. Interestingly, resveratrol exerts antineoplastic or anti-inflammatory effects and modulates expression of several miRNAs that are involved in carcinogenesis (Diaz-Gerevini et al. 2016; Kim et al. 2017). Importantly, resveratrol suppressed proliferation of breast cancer MDA-MB-231 and MCF7 cells by p53-mediated upregulation of tumor-suppressive miR-34a, miR-424, and miR-503. Apparently, upregulated miRNAs can suppress nuclear ribonucleoprotein A1 (HNRNPA1), which is responsible for tumor progression (Otsuka et al. 2018). Application of resveratrol also regulated antiapoptotic and cell cycle proteins including Bcl-2, cyclin-dependent kinases, and X-linked inhibitor of apoptosis protein mechanism by upregulation of tumor suppressive miR-125b, miR-200c, miR-542 and downregulation of miR-409 and miR-122 in breast MCF-7 and MDA-MB-231 cells (Venkatadri et al. 2016). Furthermore, effects of resveratrol on various tumor suppressive and oncogenic miRNAs were observed in mammary carcinoma of ACI rat models. After all, resveratrol upregulated expression of miR21, -129, -204, and -489 in hormone sensitive mammary tumors underlining the role of resveratrol in the suppression of tumor development and progression (Qin et al. 2014).

Sulforaphane is an isothiocyanate (SFN, 1-isothiocyanato-4-(methylsulfinyl)butane) widely distributed in cruciferous vegetable such as broccoli, cauliflower, cabbage, kohlrabi, garden cress, and bok-choy (Zhang and Callaway 2002). SFN regulates various cell cycle-associated processes including apoptosis (Li et al. 2018b). Moreover, SFN demonstrates antioxidant and anti-inflammatory potential and inhibits multiple steps of carcinogenesis, e.g. proliferation and invasiveness of tumor cells (Dacosta and Bao 2017). Recently, it was suggested that SFN may regulate the expression of miRNAs, thus exhibiting its anticancer efficacy (Pan et al. 2017). Particularly, SFN suppressed the EGFR signaling involved in EMT of non-small cell lung cancer (NSCLC) cells (H1299, 95C, 95D) via downregulation of oncogenic miR-616 targeting GSK3β/β-catenin signaling pathway, which is associated with cancer invasiveness (Wang et al. 2017). Results from another study demonstrated efficacy of SFN and iberin in the reduction of growth, invasion, and angiogenesis in CRC cell lines (NCM460, NCM356) via downregulation of miR-155 and upregulation of miR-23b and miR-27b (Slaby et al. 2013). Moreover, sulforaphane induced cell cycle arrest and senescence via decrease in expression of miR-23, miR-92b, miR-381in breast cancer cell lines (MCF-7, MDA-MB-231, SK-BR-3) (Lewinska et al. 2017). In the study of basal-like ductal carcinoma stem cells, the application of SFN dramatically decreased the levels of exosomal miRNAs-21, -140, -29a, which are involved in the promotion of tumor metastases and invasion via TNFα and IL-6 secretion (Li et al. 2014a).

Curcumin is a phytochemical dominantly found in turmeric and curry. Curcumin is effective in suppressing proliferation, invasion, and metastasis of various types of cancer cells via modulation of tumor apoptosis, increase in sensitization of cancer cells to chemotherapy, regulation of cell cycle arrest and cancer stem cells (Li et al. 2018a; Zendehdel et al. 2018). Interestingly, autocrine growth hormone (GH)

signaling induces cell growth, metastasis, and proliferation through JAK/STAT signaling pathway and transcription factor NF-κB, which is dominant mechanism of EMT in breast cancer. Eventually, treatment with curcumin suppressed proliferation and aggressive progression of cancer cells via inhibition of NF-κB signaling and downregulation of oncogenic miR-183/-96/-182 in T47D cells (Coker-Gurkan et al. 2018). Furthermore, an expression of miR-7641 directed to target p16 was suppressed by administration of curcumin which may lead to an inhibition of proliferation and invasion and, therefore, induced apoptosis in bladder cancer cell lines (T24 and SV-HUC-1) (Wang et al. 2018b). Curcumin also inhibited colon cancer proliferation in SW480 cells via upregulation of miR-130a levels, which attenuated cell proliferation by repressing Wnt/β-catenin pathway (Dou et al. 2017). Antitumorigenic effects of curcumin were also evaluated in SCID mice xenograft tumor model of glioblastoma multiforme. Results of the study revealed that an increase in the level of miR-378 inhibited cellular growth by targeting p38, thus enhancing treatment effects of curcumin (Li et al. 2017b).

A natural isoflavonoid genistein (4′,5,7-trihydroxyisoflavone) is a major compound of soy-based foods. Recently, the intake of rich-soy diet was associated with anticancer efficacy (Spagnuolo et al. 2015; Varinska et al. 2015). Oncogenic miR-155 is one of the major miRNAs which are upregulated in various types of tumors. Interestingly, invasiveness and metastasis were inhibited by administration of genistein in MCF-7 and MDA-MB-435 breast cancer cell lines via downregulation of miR-155 and upregulation of its targets (*FOXO3, PTEN*, casein kinase, and p27) (de la Parra et al. 2016). Moreover, genistein inhibited retinoblastoma cell (Y79) viability and cellular growth via upregulation of miR-145 and suppression of target gene *ABCE1*, a member of superfamily of ATP-binding cassette (ABC) transporters which are responsible for active transport molecules through phospholipids bilayer (Wei et al. 2017). Another study evaluated effects of genistein on the inhibition of the growth of breast cancer cells (MCF-7 cells) via miR-23b upregulation. Increased levels of miR-23b may lead to cytoskeletal reorganization and reduces invasion via suppression of PAK2 gene (Avci et al. 2014).

Ellagic acid (EA) or 2,3,7,8-tetrahydroxychromeno[5,4,3-cde]chromene-5,10-dione is a dietary phenol found in numerous fruits and vegetables, whose antitumor effects were documented (Derosa et al. 2016). EA downregulated expression of oncogenic miR-224 in colon cancer cells, which led to the stabilization of p21, whereas expression of miR-215 suppressed carcinogenesis via modulation of p53 through p21 accumulation (González-Sarrías et al. 2016). Additionally, EA suppressed mammary gland cancer progression in ACI rat model upon estrogen exposure. EA inhibited estrogen-mediated carcinogenesis by upregulation of miR-183, miR-205, and miR-375 and downregulation of miRNA-122, miR-127, and miR-182, thus modulating their target proteins ERα, CCND1, RASD1, FoxO3a, FoxO1, CCNG1, Bcl-2, and Bcl-w (Munagala et al. 2013).

Indole-3 carbinol (I3C) is a phytochemical, which is similarly as SFN, derived from vegetables of family cruciferae and possesses antineoplastic activity against various tumors (Lee et al. 2018). The correlation between regulation of tumor-suppressive miRNA-34a and inhibition of proliferation was monitored in breast cancer cell lines (MCF-7, T47D) treated with I3C. Interestingly, I3C upregulated miR-34a expression and effectively suppressed cancer progression via regulation of p53 (Hargraves et al. 2015). Importantly, I3C inhibited AKT pathway and promoted expression of phosphatase and tensin homolog (*PTEN*) in hepatocellular carcinoma (HCC) xenografted nude mice and HCC cell lines SK-Hep-1 and SNU-449 via downregulation of miR-21 (Wang et al. 2014b). In summary, anticancer effects of phytochemicals targeting miRNAs in preclinical research are well documented (Table 2).

Clinical studies

The potential of phytochemicals in regulation of miRNA expression is documented in previously mentioned in vitro or animal studies. However, only a few studies deal with antitumor efficacy of phytochemicals regulating expression of miRNAs in clinical trials. Interestingly, BR-DIM is a formulated 3,3′-diindolylmetahne (DIM) derived from the digestion of I3C. In phase II clinical study, an expression of tumor suppressive miRNA-34a was evaluated in human prostate cancer after BR-DIM treatment via demethylation of miR-34a promotor region. Increased expression of mir-34a correlated with decrease in the expression of androgen receptor (AR), while lower expression of miR-34 correlated with upregulation of Notch-1 or CD44. Consequently, BR-DIM intervention led to increase in miRNA-34a level, especially in patient with higher Gleason grade tumors (evaluation of aggressiveness of prostate cancer) (Kong et al. 2012). Moreover, a randomized study focused on the association between high red meat (HRM) consumption and upregulation of the oncogenic miR-21 and miR17–92 cluster compared to supplementation with butyrylated resistant starch (HRM + HAMSB) in the rectal mucosa of healthy volunteers. Based on the results, the study demonstrated that expression of miR17–92 cluster was downregulated, but level of miR-21 remained higher when compared with basal expression after HRM + HAMSB intervention. Alterations in miRNA expression in response to HRM diet were significantly associated with downregulation of their target mRNAs that are encoded by gene *CDKN1A*. Accordingly, resistant starch consumption may reduce the risk associated

Table 2 Phytochemicals involved in miRNA regulation of carcinogenesis in preclinical studies

Phytochemical	Cell line/animal model	MiRNA-regulation	References
EGCG	CNE2	↑ miR-1202; ↑ miR-1207-5p; ↑ miR-1225-5p; ↑ miR-1915; ↑ miR-1973; ↑ miR-210; ↑ miR-2861; ↑ miR-3162; ↑ miR-3196; ↑ miR-34a; ↑ miR-3656; ↑ miR-3665; ↓ miR-205-3p	Li et al. (2017a)
	B16	↑ miR-let-7-b	Yamada et al. (2016)
	A/J mice	↑ miR-210	Zhou et al. (2014)
Resveratrol	MDA-MB-231; MCF7	↑ miR-34a; ↑ miR-424; ↑ miR-503	Otsuka et al. (2018)
	MDA-MB-231; MCF7	↓ miR-125b; ↓ miR-200c; ↑ miR-409; ↑ miR-122; ↓ miR-542	Venkatadri et al. (2016)
	Female ACI rats	↑ miR-21; ↑ miR-129; ↑ miR-204; ↑ miR-489	Qin et al. (2014)
Sulforaphane	H1299; 95C; 95D	↓ miR-616	Wang et al. (2017)
	NCM460; NCM356	↓ miR-155; ↑ miR-23b; ↑ miR-27b	Slaby et al. (2013)
	MCF-7, MDA-MB-231, SK-BR-3	↓ miR-23; ↓ miR-92b; ↓ miR-381	Lewinska et al. (2017)
	DCIS stem-like cells	↓ miR-21; ↓ miR-140; ↓ miR-29a	Li et al. (2014a)
Curcumin	T47D	↓ miR-183/-96/-182	Coker-Gurkan et al. (2018)
	T24; SV-HUC-1	↓ miR-7641	Wang et al. (2018b)
	SW480	↑ miR-130a	Dou et al. (2017)
	SCID mice	↑ miR-378	Li et al. (2017b)
Genistein	MCF-7; MDA-MB-435	↓ miR-155	de la Parra et al. (2016)
	Y79	↑ miR-145	Wei et al. (2017)
	MCF-7	↑ miR-23b	Avci et al. (2014)
Ellagic acid	Caco-2, HT-29	↑ miR-215; ↓ miR-214	González-Sarrías et al. (2016)
	ACI rats	↓ miR-182; ↑ miR-183; ↑ miR-375; ↓ miR-122; ↓ miR-127; ↑ miR-205	Munagala et al. (2013)
Indole-3 carbinol	MCF-7; T47D	↑ miR-34a	Hargraves et al. (2015)
	SK-Hep-1; SNU- 449 Female athymic nude mice	↓ miR-21	Wang et al. (2015)

Explanatory notes: ↑ increase, ↓ decrease

with HRM diet (Humphreys et al. 2014). Furthermore, a clinical study on 272 triple negative breast cancer patients demonstrated protective effects of long-term soy intake against breast cancer development. Authors evaluated the expression of total 800 miRNAs involved in the mechanisms regulating cancer progression. Consumption of soy led to a modulation of several miRNAs which are associated with carcinogenesis including miR-29a-3p, -223-3p, -142-3p, -150-5p, -590-3p, -219-5p, -3690, -188-3p, -3168, -2110, -759, -891b, and -4421. Target genes of the already mentioned miRNAs include *TP53*, *AGO2,* and *DDX20,* which are significantly involved in the regulation of cell growth, invasiveness, and proliferation (Guo et al. 2016). Furthermore, a study by Tarallo et al. (2014) analyzed different expression profiles of several miRNAs-16, -21, -34a, -222, and -92a in plasma and stool sample in three groups of volunteers with different dietary habits (vegetarian, vegan, and omnivorous). Results of this pilot study revealed upregulation of tumor suppressive miR-92a in groups of vegans and vegetarian when compared to omnivorous group; moreover, significant association with lower BMI was also demonstrated. Therefore, specific dietary habits may correlate to different miRNA expression profiles that are involved in the initiation of various diseases including cancer (Tarallo et al. 2014). There are numerous clinical studies which confirmed antineoplastic potential of naturally occurring bioactive compounds from plants or dietary supplements, but only few of them focus on the role of miRNAs in the carcinogenesis.

As described previously, numerous phytochemicals and functional foods showed anticancer efficacy via targeting miRNAs in preclinical and clinical studies (Fig. 3).

Conclusion and future perspectives

Data suggest that irregularities in the miRNA expression leads to conditions that are associated with cancer, including modulation of proliferation, cell death, migration, invasion, EMT, hypoxia, self-renewal, and tumor angiogenesis. Moreover, miRNAs can act as regulators of cancer cell

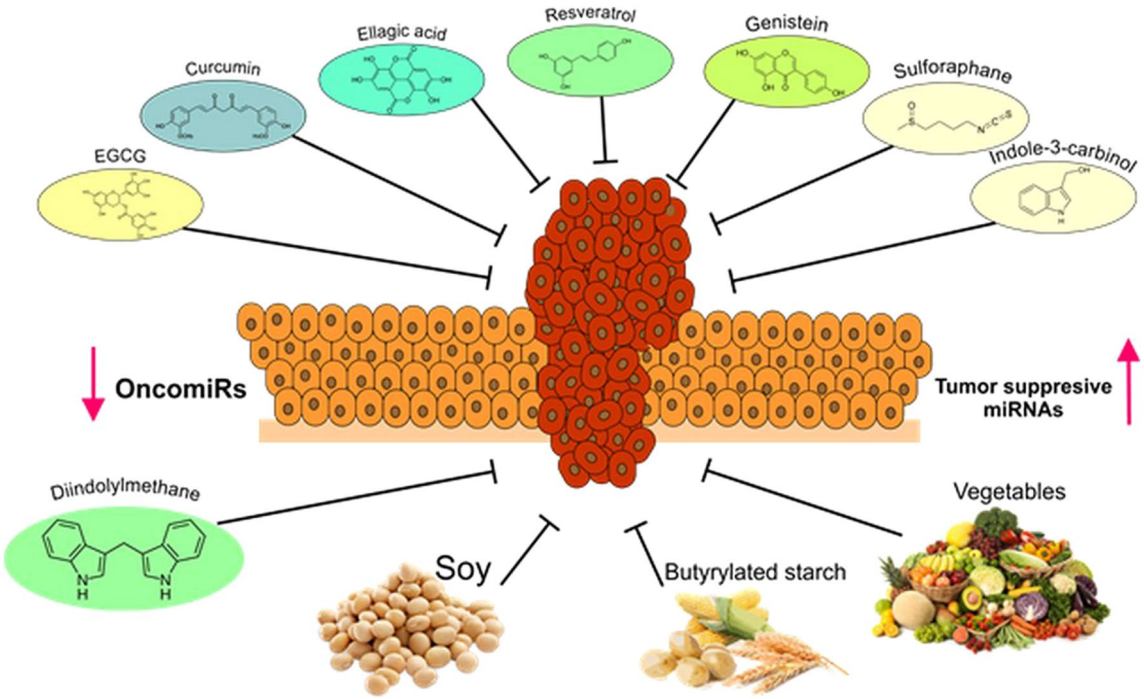

Fig. 3 Phytochemicals and functional foods targeting cancer progression via miRNA regulation in preclinical and clinical cancer research (Avci et al. 2014; Coker-Gurkan et al. 2018; de la Parra et al. 2016; Dou et al. 2017; González-Sarrías et al. 2016; Guo et al. 2016; Hargraves et al. 2015; Humphreys et al. 2014; Kong et al. 2012; Lewinska et al. 2017; Li et al. 2014a, 2017a, b; Munagala et al. 2013; Otsuka et al. 2018; Qin et al. 2014; Slaby et al. 2013;Tarallo et al. 2014; Venkatadri et al. 2016; Wang et al. 2015, 2017, 2018b; Wei et al. 2017; Yamada et al. 2016; Zhou et al. 2014). Isolated phytochemicals including epigallocatechin-3-gallate (EGCG), curcumin, ellagic acid, resveratrol, genistein, suplforaphane, indol-3-carbinol (EA), Diindolylmethane (DIM), and plant functional foods including soy, foods with butyrylated starch, and vegetarian or vegan foods demonstrated antineoplastic properties via regulation of miRNAs involved in invasiveness, proliferation, migration, EMT, hypoxia or angiogenesis. The majority of significant results were observed in preclinical trials. Clinical trials demonstrated modulatory properties of single phytochemicals or functional plant foods in regulation of miRNA expression but further research is needed

chemoresistance to various treatment approaches. Recent evidence from clinical and experimental studies demonstrated that phytochemicals (isolated or functional foods) have antioxidant, antineoplastic, and antiangiogenics effects against various cancer types. The ability of phytochemicals to regulate miRNA expression is mediated through different mechanisms including epigenetic modification. This review summarizes the antineoplastic effects of phytochemicals in experimental studies and their possible application in clinical management of concern with significant differences in the expression of tumor suppressive and oncogenic miRNAs in various cancer types. Moreover, protective effects of phytochemicals such as curcumin, resveratrol, sulforaphane, epigallocatechin 3 gallate, genistein, ellagic acid, and indole-3 carbinol or functional foods were emphasized in numerous experimental in vivo/in vitro studies and in clinical trials. Regulatory effects of phytochemicals predict them for therapeutic applications in combination with conventional medicine with the aim to improve effectiveness of cancer treatment. On the other hand, some phytochemicals and essential nutrients with potential pro-cancer effects can regulate particular pathways leading to promotion of carcinogenesis through upregulation of oncomiRNAs. These natural compounds and dietary factors associated with cancer progression are frequently included in the human dietary habits. Therefore, discovering their interactions with epigenetic mechanisms, including aberrant expression of miRNAs, is needed. Currently, the majority of the evidence consists of preclinical studies and only a few clinical trials focus on phytochemicals regulating the expression of miRNAs in association with carcinogenesis. In conclusion, aberrant expression of miRNAs promotes initiation and progression of various malignancies. However, phytochemicals as important regulators of miRNA expression are associated with epigenetic regulations and modulation of several genes involved in cancer progression. Importantly, higher intake of food rich in phytochemicals may represent a perspective approach in the cancer chemo-preventive clinical programs.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Patients have not been involved in the study.

Human and animal rights No experiments have been performed including patients and/or animals.

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