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Review Article

miRNA as molecular target of polyphenols underlying their biological effects

Dragan Milenkovic*, Baptiste Jude, Christine Morand

INRA, UMR 1019, UNH, CRNH Auvergne, F-63000 Clermont-Ferrand, Clermont Université, Université d'Auvergne, Unité de Nutrition Humaine, BP 10448, F-63000 Clermont-Ferrand, France

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ABSTRACT

Polyphenols are the most abundant antioxidants in the human diet and are widespread constituents of fruits and beverages, such as tea, coffee, and wine. Epidemiological, clinical, and animal studies support a role of polyphenols in the prevention of various chronic diseases. For a long time, their direct antioxidant effect has been reported as the mechanism responsible for the observed health properties. However, recent findings revealed that polyphenols could interact with cellular signaling cascades regulating the activity of transcription factors and consequently affecting the expression of genes. Together with this classical regulatory pathway, polyphenols have been shown to affect the expression of microRNAs (miRNA). miRNAs are small, noncoding RNAs implicated in the regulation of gene expression that control both physiological and pathological processes such as development and cancer. Furthermore, expression of miRNAs can be affected by different external stimuli including nutrients such as vitamins, lipids, and phytochemicals. In this paper, we review studies assessing modulation of miRNAs expression by dietary polyphenols that could constitute a new pathway by which these compounds may exert their health effects. Over 100 miRNAs, involved in the control of different cellular processes such as inflammation or apoptosis, were identified as modulated by polyphenols. Most of the studies were performed in vitro using different cell lines, particularly cancer cell lines, and few studies were performed in animals. From all these data, miRNAs appear as interesting mediators in regulating polyphenols' biological effects; however, further studies are needed to validate miRNA targets and particularly in physiologically relevant conditions taking into account the bioavailability of dietary polyphenols.

Contents

Abbreviations: EGCG, (−)-epigallocatechin-3-gallate; 5-CQA, 5-*O*-caffeoylquinic acid

* Corresponding author at: INRA centre de recherche de Clermont-Ferrand/Theix, Unité de Nutrition Humaine (UNH), Equipe Micronutriments, métabolisme et santé (MiMeS), 63 122 Saint-Genès-Champanelle, France.
E-mail address: dragan.milenkovic@clermont.inra.fr (D. Milenkovic).

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Introduction

In the context of human nutrition in Western countries we face the reality of nutritional imbalances associated with high-energy intake in parallel with inadequate micronutrient intakes. One interesting challenge for research is to address the causal relationships between diet and health by examining the specific role of micronutrients in the protective effect of complex foods on human health. Although there is much evidence to support the benefits of a diet rich in plant foodstuffs (fruits, vegetables, legumes, seeds) [1], evidence that these effects are due to specific nutrients or micronutrients is limited. In addition, the question arises about the health value of nonessential micronutrients (polyphenols, carotenoids, phytosterols, etc.), and their contribution to the health effects associated with some plant foods and dietary patterns (Mediterranean, Cretan, vegetarian, etc.). Defining the role of these phytochemicals in the maintenance of health and prevention of diseases requires a good knowledge of their fate in the body (bioavailability, metabolism), their physiological effects, and the identification of their cellular and molecular targets.

Polyphenols are the most abundant phytochemicals in fruits, vegetables, and plant-derived beverages. They represent a wide variety of compounds divided into several classes according to their chemical structures, i.e., phenolic acids (hydroxybenzoic acids (C6–C1) and hydroxycinnamic acids (C6–C3)), flavonoids (C6–C3–C6, including six subclasses: anthocyanins, flavanols, flavonols, flavones, flavanones, and isoflavones), stilbenes (C6–C2–C6), lignans (C6–C3–C3–C6), and curcuminoids (C6–C3–C1–C3–C6). With the recent development of comprehensive databases on the content of polyphenols in foods, the average daily intakes were estimated in the range of 1 to 1.2 g/day for total polyphenols; 40% consisted of flavonoids [2,3]. Most of the polyphenols rarely occur in foods as unconjugated aglycones but rather as conjugates with sugars or organic acids or as polymers for flavonoids [4]. During absorption, dietary polyphenols are extensively metabolized by the gut microbiota and then by intestine and liver and consequently the predominant (and very often exclusive) forms that reach the blood and target tissues are conjugated metabolites (mainly glucuronidated, sulfated, and methylated derivatives), chemically distinct from the parent compounds found in plant foods. Maximum concentrations of flavonoids in plasma are usually reached between 1 and 6 h after consumption. The maximum concentration in plasma rarely exceeds 1 μM after the consumption of 50 mg of a single phenolic compound and the extent of absorption was quite variable with relative urinary excretion ranging from 0.3 to 43% of the ingested dose depending on the polyphenol [5]. So far, there is no convincing evidence for long-term accumulation of water-soluble metabolites even when high doses of polyphenols are consumed repeatedly [4].

Epidemiological studies suggest that a high intake of fruits and vegetables rich in polyphenols may be associated with a decreased risk of a range of human chronic disorders including cardiovascular disease, inflammatory and metabolic diseases, neurodegenerative diseases, and some cancers [6–9]. These phytochemicals have been strongly linked with beneficial effects in many clinical, animal, and in vitro studies. With respect to cardiovascular health and metabolic diseases, they may alter lipid metabolism, reduce LDL oxidation, slow down atherosclerotic lesion development, improve endothelial function, decrease blood pressure, inhibit platelet aggregation, improve insulin resistance, and regulate inflammation [10–12]. Polyphenols, particularly flavonoids, have also been shown to exert beneficial cognitive effects and to reverse age-related neurodegenerative declines [13]. They also exhibit a variety of anticarcinogenic effects, mediated through inhibition of cancer cell proliferation, regulation of apoptosis, and prevention of angiogenesis and tumor cell proliferation [14].

Unlike many pharmacological compounds specifically acting on a receptor or signaling pathway, polyphenols have most often multitarget actions. Depending on the compounds, polyphenols may act through nonspecific and/or specific mechanisms [15]. The first concern their ability to interact with plasma membranes, leading to changes in their structure and physical characteristics that could affect cell function. The second are based on particular structural and conformational characteristics of select polyphenols and their biological target, including their ability to modulate enzyme activities and transcription factors or to interact with receptors. The diversity of these potential mechanisms of action explains the wide spectrum of biological activities associated with polyphenols, among which are anti-inflammatory, antioxidant, antiproliferative, or pseudoestrogenic. The complexity of these mechanisms of action cannot be addressed efficiently by using only targeted approaches. That is why in recent years, the use of nutrigenomics has allowed great advances in deciphering the molecular and cellular mechanisms underlying their protective effects, mainly regarding cardiovascular health [16–20]. In particular, microarray studies have revealed molecular targets common to a wide range of polyphenols. Thus, the antiatherogenic or vascular protective effects induced by dietary interventions with isolated polyphenols in animal models of atherosclerosis and in humans have been associated with changes in expression of numerous genes involved in the early steps of vascular dysfunction and atherosclerosis. These studies have also provided new insights into the signaling pathways, transcription factors, and other potential regulators (including miRNA) involved in the control of gene expression by polyphenols.

MicroRNAs (miRNAs) are endogenous, noncoding, single-stranded RNAs of 22 nucleotides and constitute a class of gene regulators [21]. MiRNAs are initially transcribed by RNA polymerase II (Pol II) in the nucleus to form large pri-miRNA transcripts that are processed by the RNase III enzymes, Drosha and Dicer, to generate 18- to 24-nucleotide mature miRNAs [22]. More than 700 miRNAs have been cloned and sequenced in the human [23] and it is believed that miRNAs control the posttranscriptional regulation of 30% of mammalian genes [24]. The mature miRNAs negatively regulate gene expression depending on the degree of complementarity between the miRNA and its target; miRNAs that bind to the 3′ UTR of mRNA with imperfect complementarity block protein translation, while miRNAs that bind to mRNA with perfect complementarity induce targeted mRNA cleavage. Through modifying the availability of mRNAs and in consequence protein synthesis, miRNAs control many cellular processes, such as cell differentiation, growth, proliferation, and apoptosis [25]. Changes in miRNAs expression profiles are being extensively studied in human diseases, such as cancer, skeletal muscle diseases, or cardiovascular diseases [26–31]. It has been also reported that some nutrients in foods, such as vitamins, amino acid, fatty acids, retinoic acid, and folate can modulate miRNA expression [32–35]. The aim of the present paper is to review the current knowledge on the impact of polyphenols on expression of miRNAs.

Impact of polyphenols on miRNA expression

Most studies performed to date have been performed in vitro using native polyphenols at high concentrations rather than metabolites present in the circulation in low concentration, while only few in vivo studies using different animal models have been reported. Furthermore, the published studies implement molecules belonging to different classes of polyphenols and whose detailed chemical structures are shown in Fig. 1.

Flavonoids

Flavanols

Flavanols are a class of flavonoids including monomeric and oligomeric, known as proanthocyanidins, forms of catechins, commonly present in green teas, cocoa, and various fruits. A number of epidemiological, clinical, and experimental studies have indicated the potential role of flavan-3-ols in prevention of different diseases. (−)-Epigallocatechin-3-gallate (EGCG) is a major polyphenol found in green tea and possesses potential anticancer and cardiovascular protective properties [36–38]. It has been shown that EGCG, at 50 μM for 24 h, decreased expression of oncogenic miRNAs (mir-92, miR-93, and mir-106b) and at the same time increased expression of tumor-suppressor miRNAs (miR-7-1, miR-34a, and miR-99a) in both human malignant neuroblastoma SK-N-BE2 and IMR-32 cell lines [39] (Table 1). In the mouse lung adenocarcinoma cell line CL13, EGCG, at 40 μM, increased expression of miR-210 and decreased cell growth, suggesting that the modulation of expression of this miRNA could contribute to the anticancer activity of this flavonoid [40]. Interestingly, the use of a holistic approach, that is, microarray containing primers of all known miRNAs, has shown that EGCG at 100 μM can modulate expression of 61 miRNAs simultaneously in human hepatocellular carcinoma HepG2 cells [41]. Among these miRNAs, the expression of 13 was identified as up-regulated while the expression of 48 was identified as down-regulated, and the observed miRNA expression profile was associated with EGCG-induced apoptosis. One more recent study has reported that EGCG,

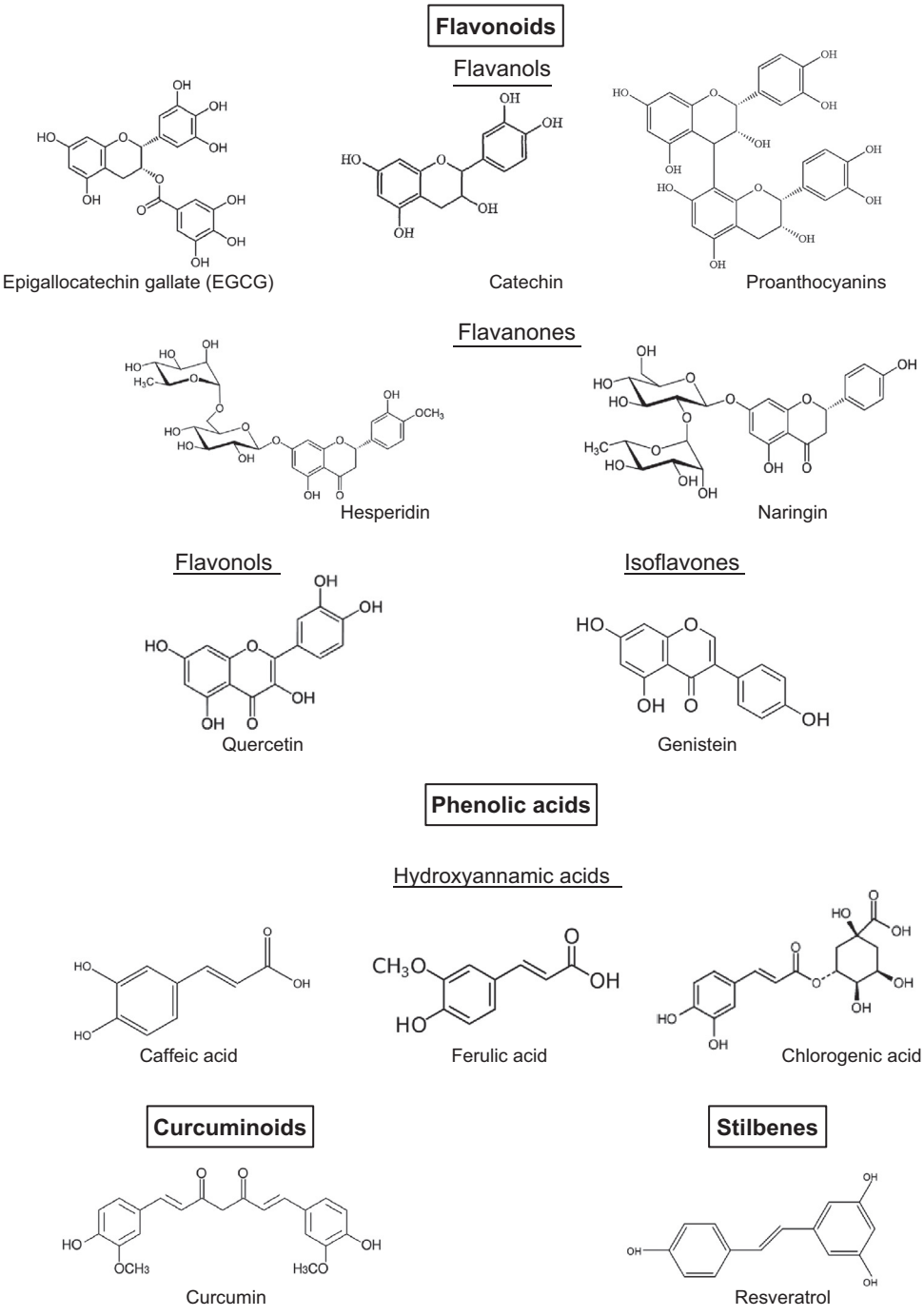

Fig. 1. Chemical structures of polyphenols discussed in this review regarding their capacity to modulate expression of miRNAs.

Table 1
miRNA regulated by polyphenols in vitro and in vivo.

Polyphenol	*Compound*	*Experimental model*	*Concentration/ dose*	*Duration*	*Method analysis*	*miRNA*	*Reference*
Flavonoids							
Flavanols							
	EGCG	human neuroblastoma cells	50 μM	24 H	RT-PCR	mir-92,,miR-93,,mir-106b,,miR-7-1,,miR-34a,,miR-99a	39
	EGCG	mouse adenocarcinoma cells	40 μM	12 H	RT-PCR	miR-210	40
	EGCG	human hepatocarcinoma cells	100 μM	24 H	microarrays	miR-467b*,miR-487b,miR-197,miR-805,miR-374*,let-7 f, miR-350,miR-24-1*,miR-137,miR-335-3p,let-7a,miR-222, miR-26b,miR-30c-1*,let-7d,miR-98,miR-30c,miR-30b*,miR-32,miR-674*,miR-532-5p,let-7 g,miR-18a,miR-192,miR-302d,miR-30b,miR-802,let-7e,miR-322,miR-720,miR-146b, miR-340-3p,miR-185,miR-425,miR-10a,miR-126-5p,miR-101a,miR-30e*,let-7c,miR-141,miR-33,miR-29a*,miR-199b, miR-450a-5p,miR-21,miR-23a,miR-101b,miR-148a,miR-193, miR-23b,miR-107,miR-140,miR-551b,miR-466c-5p,miR-106a,miR-590-3p,miR-875-3p,miR-224,miR-292-5p,miR-678,miR-469,let-7b*,miR-463*miR-574-3p,miR-201,miR-290-3p,miR-181a,miR-302a,miR-429,miR-133a,miR-190b, miR-710,miR-135b,miR-296-5p,miR-191*,miR-188-5p,miR-298,miR-181a-1*,miR-466 g,miR-26b*,miR-466 f-3p,miR-29b*,miR-1224,miR-291b-5p,miR-324-5p,miR-486,miR-128, miR-450b-3p,miR-135a*,miR-294,miR-671-5p,miR-878-3p, miR-801,miR-370,miR-1,miR-494,miR-133b,	41
	EGCG	nude mice	1 mg/day	3 days/ week 6 weeks	RT-PCR	miR-21,miR-330	43
	catechin	apo E-/- mice	30 mg/day	2 weeks	microarrays	miR-326,miR-129-3p,miR-149,miR-31*,miR-34a,miR-483*, miR-345-5p,miR-31,miR-677,miR-24-1*,miR-17,miR-181b, miR-802,miR-214,miR-671-5p,miR-18a,let-7b*,miR-429, miR-423-5p,miR-676,miR-669a,miR-702,miR-877*,miR-376b*,miR-298,miR-128,let-7 f*,miR-190b,miR-200c,miR-324-5p,miR-133a,miR-302a,miR-715,miR-290-3p,miR-374, miR-99b,miR-144,miR-451,miR-296-5p,miR-191*,miR-486, miR-291b-5p,miR-133b,miR-1,miR-697,miR-197,miR-290-5p,miR-467b*,miR-125a-3p,miR-30b*,miR-212,miR-30c-1*, miR-466c-5p,miR-680,miR-139-3p,miR-374*,miR-455*,miR-487b,miR-335-3p,miR-202-3p,miR-705,miR-136,miR-196b, miR-335-5p,miR-32,miR-721,miR-302d,miR-146b,miR-141, miR-154,miR-294,miR-137,miR-450a-5p,miR-126-5p,miR-551b,miR-690,let-7c-2*,miR-196a,miR-669c,miR-186*	45
	proanthocyanins	apo E-/- mice	300 mg/day	2 weeks	microarrays	let-7b*,let-7c-2*,miR-1,miR-106a,miR-125a-3p,miR-133a, miR-133b,miR-146b,miR-17,miR-181a,miR-190,miR-190b, miR-191*,miR-196a,miR-196b,miR-197,miR-200c,miR-291b-3p,miR-291b-5p,miR-292-5p,miR-294,miR-296-5p,miR-297a,miR-29a*,miR-302a,miR-302b,miR-302c,miR-302d, miR-30c-1*,miR-324-5p,miR-335-3p,miR-374,miR-374*, miR-450a-3p,miR-450b-5p,miR-455*,miR-464,miR-467b*, miR-469,miR-483*,miR-486,miR-487b,miR-505,miR-539, miR-542-3p,miR-551b,miR-669a,miR-671-5p,miR-676,miR-698,miR-7b,miR-801,miR-878-3p,miR-881,miR-99b	45
Flavonols							
	quercetin	murine RAW264.7	10 μM		RT-PCR	miR-155	48
	quercetin	mice C57B6/j	2 mg/g of diet	6 weeks	RT-PCR	miR-122,miR-125b	49
	quercetin	apo E-/- mice	30 mg/day	2 weeks	microarrays	miR-486,miR-375,miR-181a,miR-541,miR-324-5p,miR-210, miR-702,miR-211,miR-298,miR-423-5p,miR-715,miR-296-5p,miR-21*,miR-429,miR-671-5p,miR-99b,miR-466 f-3p, miR-878-3p,let-7b*,miR-128,let-7 f*,miR-290-3p,miR-451, miR-291b-5p,miR-144,miR-197,miR-30b*,miR-467b*,miR-450a-5p,miR-30c-1*,miR-190,miR-1,miR-466c-5p,miR-374*, miR-7b,miR-455*,miR-680,miR-29a*,let-7c-2*,miR-872, miR-29b*,miR-196b,miR-196a,miR-335-5p,miR-137,miR-335-3p,miR-10b	45

Table 1 (*continued*)

Polyphenol	*Compound*	*Experimental model*	*Concentration/ dose*	*Duration*	*Method analysis*	*miRNA*	*Reference*
Flavanones							
	hesperidin	apo E-/- mice	30 mg/day	2 weeks	microarrays	let-7a,let-7b*,let-7c,let-7d,let-7e,let-7 f,let-7 g,miR-1,miR-101a,miR-101b,miR-106a,miR-107,miR-10a,miR-1224,miR-126-5p,miR-128,miR-133a,miR-133b,miR-135a*,miR-135b, miR-137,miR-140,miR-141,miR-146b,miR-148a,miR-181a, miR-181a-1*,miR-185,miR-188-5p,miR-18a,miR-190b,miR-191*,miR-192,miR-193,miR-197,miR-199b,miR-201,miR-21, miR-222,miR-224,miR-23a,miR-23b,miR-24-1*,miR-26b, miR-26b*,miR-290-3p,miR-291b-5p,miR-292-5p,miR-294, miR-296-5p,miR-298,miR-29a*,miR-29b*,miR-302a,miR-302d,miR-30b,miR-30b*,miR-30c,miR-30c-1*,miR-30e*, miR-32,miR-322,miR-324-5p,miR-33,miR-335-3p,miR-340-3p,miR-350,miR-370,miR-374*,miR-425,miR-429,miR-450a-5p,miR-450b-3p,miR-463*,miR-466c-5p,miR-466 f-3p,miR-466 g,miR-467b*,miR-469,miR-486,miR-487b,miR-494,miR-532-5p,miR-551b,miR-574-3p,miR-590-3p,miR-671-5p,miR-674*,miR-678,miR-710,miR-720,miR-801,miR-802,miR-805, miR-875-3p,miR-878-3p,miR-98	45
	narangin	apo E-/- mice	30 mg/day	2 weeks	microarrays	let-7c-2*,miR-106a,miR-10b,miR-125a-5p,miR-132,miR-133a,miR-135a*,miR-139-3p,miR-141,miR-146b,miR-150, miR-154,miR-155,miR-17,miR-181a,miR-186*,miR-188-5p, miR-18a,miR-190,miR-196a,miR-196b,miR-197,miR-210, miR-214,miR-219,miR-290-5p,miR-291b-3pmiR-291b-5pmiR-294miR-296-5pmiR-298miR-29a*miR-302dmiR-30b*,miR-30c-1*miR-31,miR-324-5p,miR-335-3p,miR-335-5p,miR-34a,miR-374,miR-374*,miR-450a-5p,miR-451,miR-455,miR-455*,miR-466c-5p,miR-466 f-3p,miR-467b*,miR-483,miR-486,miR-494,miR-541,miR-542-3p,miR-551b,miR-574-3p,miR-669a,miR-671-5p,miR-676,miR-680,miR-689, miR-706,miR-712,miR-721,miR-7b,miR-801,miR-877,miR-878-3p,miR-99b	45
Isoflavones							
	genistein	human prostate cancer cells	25 μM	4 days	RT-PCR	miR-151a-3p,miR-151-5p	54
	genistein	human ovarian cancer cell	5 M	48 H	microarrays	miR-100,miR-122a,miR-125b,miR-126,miR-135,miR-135b, miR-136,miR-137,miR-141,miR-152,miR-190,miR-196a,miR-196b,miR-204,miR-205,miR-206,miR-217,miR-22,miR-296, miR-30a-3p,miR-30a-5p,miR-331,miR-335,miR-342,miR-362,miR-449b,miR-454,miR-497,miR-500,miR-501,miR-503, miR-515,miR-517c,miR-532,miR-565,miR-578,miR-584,miR-585,miR-590,miR-595,miR-625,miR-647,miR-7,miR-765, miR-766	55
Phenolic acids							
	5-O-caffeoylquinic acid	mice hepatoma cells	5 μM	24 H	RT-PCR	miR-122	64
	caffeic acid	apo E-/- mice	300 mg/day	2 weeks	microarrays	let-7b*,miR-1,miR-125a-3p,miR-137,miR-191*,miR-196a, miR-196b,miR-197,miR-222,miR-24-1*,miR-291b-5p,miR-296-5p,miR-298,miR-29a*,miR-30b*,miR-30c-1*,miR-31*, miR-328,miR-335-3p,miR-374*,miR-429,miR-455*,miR-466c-5p,miR-467b,miR-467b*,miR-467c,miR-532-5p,miR-574-3p,miR-669c	45
	ferulic acid	apo E-/- mice	300 mg/day	2 weeks	microarrays	let-7b*,let-7c-2*,let-7 f*,miR-1,miR-146b,miR-149,miR-155, miR-15b*,miR-191*,miR-196b,miR-200c,miR-21*,miR-24-1*, miR-291b-3p,miR-291b-5p,miR-296-5p,miR-298,miR-29a*, miR-302d,miR-30b*,miR-30c-1*,miR-324-5p,miR-326,miR-374,miR-374*,miR-423-5p,miR-429,miR-450a-5p,miR-466 f-3p,miR-467b*,miR-483*,miR-541,miR-574-3p,miR-674*, miR-712,miR-801,miR-802,miR-877,miR-878-3p	45
	ellagitannin	human hepatocarcinoma cells	50 μg/ml	6 H	microarrays	miR-302a*,miR-194,miR-433,miR-424,miR-510,miR-519e*, miR-370,miR-526b,miR-373*,miR-525,let-7e,miR-346,miR-518 f*-526a,miR-452,miR-518c*,miR-512-5p,miR-513,iR-200a*,let-7i,let-7 f,miR-299-3p,miR-542-3p,let-7d,let-7c, let-7a	65

Table 1 (*continued*)

Polyphenol	*Compound*	*Experimental model*	*Concentration/ dose*	*Duration*	*Method analysis*	*miRNA*	*Reference*
Curcuminoids							
	curcunim	human colon carcinoma cells	30 μM	24 H	RT-PCR	miR-27a,miR-20 A,miR-17-5 P	69
	curcunim	human colon carcinoma cells	10-20 μM		RT-PCR	miR-21	70
	curcunim	human bladder carcinoma cells	10 μM	3 days	RT-PCR	miR-203	71
	curcunim	human lung adenocarcinoma cells	10 μM	48 H	microarrays	miR-320,miR-26a,let-7i,miR-130a,mir-16,miR-125b,miR-23a,miR-27b,miR-155,miR-625,miR-576-3p,miR-186*,miR-9*,met-7e	72
	curcunim	human leukemia and primary leukemic cells	5-20 μM	24-72 H	RT-PCR	miR-15a,miR-16-1	73
	curcunim	human pancreatic cells	10 μM	72 H	microarrays	miR-103,miR-140,miR-146b,miR-148a,miR-15b,miR-181a, miR-181b,miR-181d,miR-195,miR-196a,miR-199a*,miR-19a, miR-204,miR-20a,miR-21,miR-22,miR-23a,miR-23b,miR-24, miR-25,miR-26a,miR-27a,miR-34a,miR-374,miR-510,miR-7, miR-92,miR-93,miR-98	74
	curcunim	apo E-/- mice	30 mg/day	2 weeks	microarrays	let-7e,miR-1,miR-125a-5p,miR-126-5p,miR-133a,miR-135a*, miR-136,miR-137,miR-140,miR-142-3p,miR-142-5p,miR-144,miR-146a,miR-146b,miR-150,miR-154,miR-155,miR-15b,miR-181a,miR-186*,miR-188-5p,miR-190,miR-190b, miR-191*,miR-196a,miR-196b,miR-197,miR-199b,miR-19a, miR-200c,miR-21,miR-223,miR-291b-3p,miR-291b-5p,miR-296-5p,miR-29a*,miR-29b*,miR-302d,miR-30b*,miR-30c-1*,miR-31*,miR-324-5p,miR-335-5p,miR-34a,miR-362-5p, miR-374*,miR-423-5p,miR-425,miR-450a-5p,miR-451,miR-455*,miR-466c-5p,miR-467b*,miR-469,miR-483,miR-532-5p,miR-542-3p,miR-551b,miR-669c,miR-674*,miR-720,miR-7b,miR-805,miR-872,miR-877,miR-99b	45
Stilbenes							
	resveratrol	human bronchial epithelial cells	50 μM	48 H	RT-PCR	miR-622	77
	resveratrol	human monocytes cells	30 μM	14 H	microarrays	miR-155,miR-633	78
	resveratrol	human lymph node cancer prostate	50 μM	48 H	microarrays	let-7c,miR-106a,miR-106b,miR-1224-5p,miR-1228,miR-1231,miR-1246,miR-1260,miR-1267,miR-1268,miR-129,miR-1290,miR-1308,miR-1469,miR-149,miR-150,miR-152,miR-15a,miR-17,miR-1825,miR-185,miR-18b,miR-1908,miR-1915, miR-197,miR-1972,miR-1973,miR-1974,miR-1975,miR-1977, miR-1979,miR-20a,miR-20b,miR-24,miR-296-5p,miR-483-5p,miR-513a-5p,miR-548qmiR-572,miR-575,miR-612,miR-638,miR-654-5p,miR-659,miR-671-5p,miR-7,miR-762,miR-764,miR-874,miR-92b,miR-939	79
	resveratrol	prostate carcinoma cells	25 μM	24 H	microarrays	let-7a,miR-101,miR-106a,miR-106b,miR-1274b,miR-136*, miR-141,miR-145,miR-17,miR-182,miR-1826,miR-200b,miR-200c,miR-20a,miR-20b,miR-21,miR-214,miR-221,miR-222, miR-302d*,miR-375,miR-378*,miR-720,miR-768-3p,miR-93	80
	resveratrol	human colorectal carcinoma cells	50 μM	14 H	microarrays	miR-1,miR-100-1/2,miR-102,miR-103-1,miR-103-2,miR-146a,miR-146b-5p,miR-16-0,miR-17,miR-181a2,miR-194-2, miR-196a1,miR-205,miR-206,miR-21,miR-23a,miR-23b,miR-25,miR-26a,miR-29c,miR-30a-3p,miR-30c-1,miR-30d,miR-30e-5p,miR-323,miR-340,miR-363*-5p,miR-424,miR-494, miR-497,miR-560,miR-560,miR-565,miR-565,miR-572,miR-574,miR-594,miR-615,miR-622,miR-629,miR-631,miR-638, miR-639,miR-657,miR-659,miR-663,miR-801,miR-92a-2	81
	resveratrol	Sprague-Dawley rats	5 mg/kg/day	21days	microarrays	miR-101a,miR-10a,miR-181c,miR-20b,miR-21,miR-214,miR-24-1,miR-25,miR-27a,miR-27a,miR-27b,miR-29c,miR-31, miR-324-3p,miR-339-5p,miR-345-3p,miR-345-5p,miR-351, miR-450a,miR-539,miR-667,miR-687,miR-760,miR-9	82

at 100 μM for 5 h, modulated expression of 5 different miRNAs; all of them were identified as down-regulated. Even though both studies used the same cell line, identical concentration of compound, and a microarray approach, none of the 5 miRNAs are in common with miRNA identified from the study by Tsang et al. This difference could be due to different incubation times used in the two studies (5 h versus 24 h) potentially suggesting that the impact of EGCG on miRNA expression could be dependent on the duration of exposure of cells to compounds. It is relevant to note that in vivo EGCG is present in the circulation up to 6 h and it

had been previously reported that phenolic compounds are unstable and are rapidly lost when added to cell culture medium [42]. Consequently, this instability and putative formation of oxidative products could lead to the misinterpretation of experimental observations relating to the effects of polyphenols on cell function. Interestingly, the capacity of EGCG to modulate expression of miRNA has been also observed in vivo in mice. The expression, analyzed by real-time PCR, of miR-21 and miR-330 was observed to be down-regulated and up-regulated, respectively, in mice that received EGCG for 6 weeks [43], the miRNAs that have not been identified as modulated by EGCG in in vitro studies. The discrepancy between in vitro and in vivo results could be explained by differences in concentrations used in vivo (in the range of nano or few micromolars) and in vitro studies and that EGCG can be metabolized by epithelial and hepatic cells giving rise to conjugated molecules with potentially different biological effects, such as impact on miRNA expression.

Another flavanol present in the human diet is catechin that is found in high amounts in cocoa and tea. Even though cardiovascular health effects have been largely described for this molecule [44], only one study reported the impact of catechin on miRNA expression. It has been observed that, when supplemented at a nutritionally relevant dose in a diet, catechin can modulate expression of over 80 miRNAs in the liver of apolipoprotein E-deficient mice [45]. In the same study, the authors reported that oligomeric forms of catechin, proanthocyanidis, can also modulate expression of 58 different miRNAs. Together with isolated compounds, the impact of proanthocyanidin-rich extracts from grape seed and cocoa on miRNA expression in human hepatocellular carcinoma HepG2 cells has been studied using miRNA microarrays. Grape seed extract induced changes in expression of 15 miRNAs and cocoa proanthocyanidin extract modulated expression of 6 miRNAs. Among the 6 miRNAs, 4 are in common with grape seed extract (miR-197, miR-1224-3p, mir-532-3p, and miR-30b). The absence of perfect overlap in miRNA identified with the 2 extracts could be explained by the difference in their composition regarding percentage of monomers, dimers, trimmers, and oligomers (4–6 units). Among the miRNAs identified in vitro, only 2 are in common with miRNA identified in in vivo study in liver (miR-197 and miR-483).

Flavonols

Quercetin is the major flavonoid present in the human diet that is found in different foodstuffs, such as onion, apple, or wine and exhibits a wide range of biological effects [46]. Dietary quercetin undergoes intensive intestinal and hepatic metabolization, resulting in glucuronidated, sulfated and methylated quercetin derivatives. The mechanisms underlying the biological effects observed have been related to its capacity to modulate the phosphorylation state of cell signaling molecules and consequently the expression of genes [47]. Recently, it has been shown that quercetin and its methylated metabolite, isorhamnetin, at 10 μM, can counteract LPS-induced increase in expression of miR-155 in murine RAW264.7 macrophages, while quercetin-3-glucuronide had no effect of the expression of this miRNA, which has recently been identified as a modulator of the inflammatory response [48]. Quercetin, when supplemented in the high-fat diet of C57BL/6j mice (at 2 mg/g diet) for 6 weeks, significantly increased expression of miR-125b, a negative regulator of inflammatory gene expression, and miR-122, a liver-specific miRNA involved in liver lipid metabolism and pathogenesis of liver diseases [49]. The increased expression of the 2 miRNAs was observed together with decreased expression of genes coding for CRP, IL6, and MCP1 as well as HO-1. Nontargeted analysis of miRNA expression, using microarrays, revealed that quercetin, when supplemented for 2 weeks at 0.02% in the diet, can modulate expression of a large number of miRNAs ($n=51$) in the liver of apolipoprotein E-deficient mice [45]. This study has not identified miR-122, miR-125b, nor miR-155 as in previous study; the difference in results could be explained by the fact that a different mice model (wild-type versus apolipoprotein E-deficient mice) and diet (high-fat diet versus normal diet) were used. Together with studies performed in vitro and in animal models, the impact of a quercetin-rich diet on miRNA expression in 264 lung cancer (144 adenocarcinoma and 120 squamous cell carcinoma) tissues in human has been reported [50]. The expression of 56 miRNAs was found to be significantly different between lung cancer cases from individuals who consumed high versus low quercetin-rich foods, among which are miR-146, miR-125, miR-26, and miR-17 (Table 1).

Flavanones

Flavanones represent a flavonoid subclass present in our diet, almost exclusively in citrus fruits, and present potential interest regarding cardiovascular protection [51]. To date, only one study has reported the impact of 2 major flavanones, hesperidin and naringenin, on miRNA expression in apolipoprotein E-deficient mice [45] (Table 1). Using a nontargeted approach, this study revealed that hesperidin and naringein, supplemented at a nutritionally relevant dose (30 mg equivalent in humans) per day for 2 weeks, affected the expression of 97 and 69 miRNAs respectively, with 31 miRNAs in common. These data suggest that miRNA could be also potential targets of flavanones underlying their health effects.

Isoflavones

Isoflavones are natural plant substances with structure similar to 17-β-estradiol which present positive effects on human health, in particular prevention of hormone-dependent cancers, cardiovascular diseases, osteoporosis, adverse menopausal manifestations, and age-related cognitive decline [52]. Emerging experimental evidences revealed that the mechanism underlying these health properties is related to their capacity to interact with multiple cellular signaling pathways including Akt, MAPK, Wnt, p53, and Notch signaling, and consequently regulate expression of numerous genes [53]. Recently, several studies have also revealed that isoflavones can modulate expression of miRNAs (Table 1). Exposure of prostate cancer cells to genistein at 25 μM concentration decreased the expression of oncogenic miR-151 (miR-151a-5p and miR-151a-3p) [54]. The decreased expression of this miRNA was associated with reduced cell migration and invasion as well as decreased mRNA levels of 5 target genes (N4BP1, ARHGDIA, SOX17, CASZ1, IL1RAPL1). It has also been reported that genistein, at 5 M concentration, can modulate expression of over 50 miRNAs in 2 different ovarian cancer cell lines, a mechanism linked with the inhibition of cancer cell migration and invasion [55]. These studies suggest that mediation of expression of miRNA could represent a relevant molecular mechanism underlying the health properties of isoflavones, particularly those related to prevention of cancer development.

Flavonoid-rich extracts and miRNA extraction

Together with the impact of isolated flavonoids on expression of miRNA, several studies have been performed using plant extracts rich in these compounds. Incubation of human umbilical vein endothelial cells with acaï and red muscadine grape polyphenol extract modulated the expression of miR-126 [56] while pomegranate-rich polyphenolic extract modulated the expression of miR-27a and miR-155 in a human mammary carcinoma cell line when used at a concentration of 10 μg/ml [57]. Cranberry proanthocyanidin-rich extract modulates the expression of 81 to 98 miRNAs in different esophageal adenocarcinoma cell lines

when used at 50 μg/ml [58] and green tea "polyphenon-60" was reported to affect the expression of 23 miRNAs in a human breast adenocarcinoma cell line [59]. The impact of other polyphenol extracts, such as those from *Olea europaea* [60], yaupon holly [61], and *Coptidis rhizome* [62] have been shown to affect miRNA expression in vivo and one from *Hibiscus sabdariffa* has been shown to affect the expression of these small noncoding RNAs in vivo in LDLR-/- mice [63].

Phenolic acids

The most abundant polyphenol present in coffee is 5-*O*-caffeoylquinic acid (5-CQA). It has been shown that treatment of a mouse hepatoma cell line (Hepa 1–6 cells) with 5-CQA at 5 μM significantly increased miR-122, miRNA that is highly expressed in hepatocytes and that plays an important role in regulating lipid metabolism [64] (Table 1). Using a holistic approach, another study has shown that 2 other phenolic acids, caffeic acid and ferulic acid, can modulate expression of 29 and 39 miRNAs, respectively, in the liver of apolipoprotein E-deficient mice [45]. Ellagitannin is a complex natural polyphenol compound isolated from *Balanophora japonica Makino* presenting potential antiproliferative properties. Exposure of hepatocellular cells (HepG2) to ellagitannin at 50 μg/ml for 6 h induced changes in the expression of 25 miRNAs, 17 of which have been identified as up-regulated and 8 as down-regulated, suggesting that ellagitannin can mediate, at least in part, the antiproliferative action in HepG2 cancer cells by modulating expression of these small noncoding RNAs [65].

Curcuminoids

Curcuminoids constitute another class of polyphenols, with curcumin being the main molecule that is found principally in the rhizomes of *Curcuma longa*. Curcumin has been shown to exhibit potent antioxidant, anti-inflammatory, immunomodulatory, proapoptotic, and antiangiogenic properties [66]. These effects are mediated by the capacity of curcumin to modulate the activity of signaling pathways, transcription factors, and in consequence gene expression. Epidemiological studies and clinical trials have shown an important chemoprotective effect of curcumin on colorectal and pancreatic cancers [67,68]. It has been observed that curcumin can also modulate expression of miRNA both in vitro and in vivo (Table 1). Target analysis of miRNA expression using real-time PCR revealed that curcumin (at 10–30 μM) can down-regulate the expression of pro-oncogenic miR-17-5p, miR-20a, miR-21, and miR-27a in human rectal and colon carcinoma cell lines [69,70]. This miRNA expression profile was associated with increased apoptosis, decreased cell proliferation, and tumor invasion in vitro. In other carcinoma cell lines, studies have revealed that curcumin at 10 μM can modulate the expression of miR-203 in T24 human bladder carcinoma cells [71] or down-regulate six miRNAs (miR-186*, miR-625, miR-576, miR-39, miR-9*, let7e) and up-regulate eight miRNAs (miR-320, miRNA-26a, miR-16, miRNA-130a, miR-125b, miR-23a, miR-23b, and let-7i) in human lung adenocarcinoma cells at a concentration of 15 μM [72]. In leukemia cell lines (K562 and HL-60), curcumin at a concentrations of 5–20 μM up-regulated the expression of miR-15a and miR-16-1, the genomic impact that was also observed in primary leukemic cells isolated from patients and exposed ex vivo to curcumin at 5–20 μM concentration for 24–72 h [73]. The use of miRNA microarrays revealed that curcumin (at 10 μM) can up-regulate the expression of 11 miRNAs and decrease the expression 18 miRNAs in a human pancreatic carcinoma cell line [74], suggesting that curcumin can regulate the expression of several miRNAs and not a few specific ones. Interestingly, when supplemented at nutritionally relevant concentrations, a holistic approach also revealed that curcumin can affect the expression of 67 miRNAs in the liver of apolipoprotein E-deficient mice [45]. Among these miRNAs, 8 (miR-21, miR-186, let-7i, miR-125b, miR-119b, miR-15b, miR-34a, miR-31) are in common with miRNA identified as modulated by this bioactive compound in different carcinoma cell lines.

Stilbenes

Resveratrol is the major member of the stilbene class of polyphenols found principally in grape, wine, and peanuts. This compound possesses diverse biochemical and physiological actions, including anti-inflammatory, antioxidation, antiproliferation, and promotion of differentiation, and chemopreventive effects [75]. Recently, it is attracting increased attention due to its health benefits, especially in common age-related diseases. The biological effects of resveratrol seem to be largely mediated through regulation of cell signaling pathways and expression of genes [76]. Several studies have also reported that resveratrol can modulate expression of miRNA (Table 1). When exposed to transformed human bronchial epithelial cells at 50 μM for 48 h, resveratrol up-regulated the expression of miR-622, miRNA associated with tumor suppressing properties [77]. In isolated human monocytes as well as in a THP-1 monocytic cell line, resveratrol, exposed at 30 μM for 14 h, down-regulated the expression of miR-155 and up-regulated the expression of miR-663 [78], the miRNAs involved in the regulation of cancerogenesis and inflammatory response. The use of a microarray approach revealed that resveratrol exposed at 50 μM for 24 h can affect expression of 51 miRNAs in LNCaP (lymph node cancer of prostate) [79]. Interestingly, the down-regulated miRNAs included miR-17-92 and miR-106ab clusters with well-recognized oncogenic properties while the up-regulated miRNAs included several tumor suppressors such as miR-575, miR-483, and miR-654. Similarly, when exposed to PC-3 M-MM2 (another type of prostate carcinoma cells), resveratrol, at 25 μM for 24 h, also modulated expression of miRNAs, with 10 identified as down-regulated and 15 as up-regulated [80]. A comparison of the miRNAs from the 2 studies reveals that only 5 miRNAs (miR-106a, miR-106b, miR-17, miR20a, and miR-20b) have been up-regulated in both studies. The low homology between these studies could result from the use of different cell lines, different concentrations, and time of exposure of resveratrol, revealing once again the importance of these parameters in the effect of polyphenols on miRNA expression in cells. Microarray approach has also revealed that, in human colorectal carcinoma SW480 cells, resveratrol at 50 μM can significantly increase the expression of 22 miRNAs and decrease the expression of 26 others [81]. Among the identified miRNA, several down-regulated ones are known for their oncogenic potentials, such as miR-21, while among up-regulated ones several have potential tumor-suppressor effects, such as miR-663. Taken together, most of the studies aiming to identify the impact of resveratrol on miRNA expression have been performed using in vitro models. However one study has studied the impact of this polyphenol on expression of miRNAs in vivo. The authors observed that gavage of Sprague-Dawley rats with resveratrol (5 mg/kg/day) for 21 days significantly affected the expression of 25 miRNAs in ischemia-perfused hearts [82]. Interestingly, the authors observed that most of the miRNAs in which the expression was modified following ischemia-perfusion were reversed by pretreatment with resveratrol. Principal component analysis revealed that the miRNA expression profiles of ischemia-perfused hearts pretreated with resveratrol were similar to basal level miRNA expression in heart, suggesting that resveratrol could protect the ischemic heart by restoring the IR-induced up- or down-regulation of miRNA expression.

Regulation of miRNAs transcription

Research performed during recent years has revealed the mechanisms of miRNA biogenesis and function. Nevertheless, it is evident that the expression of miRNAs themselves can be controlled; many are expressed in a tissue-specific or developmental-stage-specific manner suggesting tight and dynamic regulation of miRNA levels [83]. Still, it is poorly understood how miRNAs are transcribed and what promoter elements are used to regulate their expression [84]. Data available indicate that miRNAs transcription is probably as complex as that for any protein-expressed genes; nevertheless a small number of regulatory factors have been identified that bind to miRNA promoter elements and control their expression. It has been shown that c-Myc can regulate transcription of over 10 miRNAs such as miR-34a or miR-150 and similarly, the tumor-suppressor gene p53 can bind to promotor regions of the miR-34 family and activate their expression [84]. The capacity of polyphenols to modulate expression of miRNAs has been described in this review paper. However, the mechanisms underlying the transcriptional regulation are still unknown. It has been described that polyphenols, such as curcumin, resveratrol, ellagic acid, and black tea polyphenols, can regulate p53 activity and c-myc expression [85–87]. Taking these observations into consideration, it could be suggested that polyphenols may modulate miRNAs transcription by affecting these as well as other unknown cell-signaling proteins (Fig. 2). Furthermore, more recently, it has been shown that the miRNA biogenesis from pri-miRNA, miRNA maturation, and also miRNA decay is also regulated within the cells [84]; however, the impact of polyphenols on these processes has not been studies to date.

Conclusion and remarks

For a long time, polyphenols' health properties were attributed to the direct antioxidant effect of these phytochemicals by acting as free radical scavengers. However, the scientific community agrees that a direct antioxidant activity of these compounds beyond the gastrointestinal tract is very unlikely [88]. Recent data also revealed that polyphenols can interact with cell signaling pathways, modulate activity of transcription factors, and consequently expression of genes [89,90], suggesting that these cellular and molecular targets represent tone of the most relevant mechanisms of action underlying the beneficial effects of polyphenols. The present review demonstrates the posttranscriptional regulation of genes by polyphenols via modulation of expression of microRNAs. The potential capacity of polyphenols to modulate expression of these small noncoding RNAs has been described for compounds from different classes and subclasses, even if most of these studies deal with flavonoids and stilbenes.

The use of a holistic approach, with miRNA microarrays, revealed that polyphenols can affect the expression of numerous miRNAs and not specifically a few of them. The amount of data available is variable depending on the polyphenol classes; for instance, nine studies concerned flavonoids whereas only two used phenolic acids. Consequently, a comparison of the effects on the expression of miRNAs according to the chemical structures of polyphenols is challenging. Nevertheless, keeping this limitation in mind, a comparison of the differentially expressed miRNAs revealed that the expression of some of them seems to be polyphenol class specific while others seem to be modulated by some or all of these families (Fig. 3). Furthermore, this analysis also suggests potentially higher similarity between flavonoids and phenolic acids regarding their impact on expression of miRNAs. Based on this analysis of available data, it is difficult to go further in the characterization of the relationship between the chemical structure of polyphenols and their impact on the expression of miRNAs. As summarized in Fig. 4, miRNAs identified as modulated by polyphenols are regulating different biological functions, such as apoptosis, inflammation, anticancerogenesis, lipid metabolism, and migration. Some of these identified functions are shared between several phenolic compounds, whereas others are not. For example, miRNAs presenting anticancerogenic effects have been identified as modulated by flavonoids, stilbenes, and curcuminoids while miRNAs related to anti-inflammatory effects are modulated only by flavonoids. However, for a large number of modulated miRNAs their target processes are not still identified.

Most of the published studies have been performed in vitro and the obtained data suggest that exposition time and concentrations of compounds can differently affect the expression of miRNA. However, these in vitro results should be taken with caution for different reasons. As presented in the Introduction, most polyphenols are absorbed by the intestine where they undergo conjugation, a process that continues in the liver. Consequently, the polyphenols are present in the circulation as methylated, sulfated,

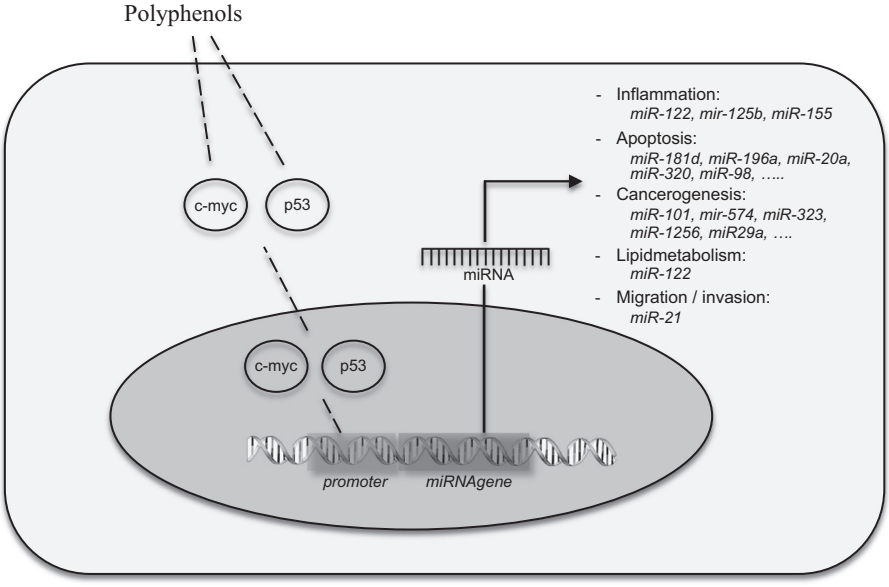

Fig. 2. Schematic representation of potential cell signaling pathways modulated by polyphenols and involved in the transcriptional regulation of miRNAs expression.

or glucuronidated conjugates, i.e., structurally different from the native molecules, in the nano to few micromolar ranges. These polyphenol conjugates are likely to possess different biological properties and distribution patterns within tissues and cells than polyphenol aglycones [91]. However, in nearly all of the studies, the native form of polyphenols or extracts rich in these compounds has been used and at high supraphysiological concentrations, up to 100 μM. Consequently, the impact of native polyphenols at high concentrations on the expression of miRNA can be different from that of their plasma metabolites at low physiologically relevant concentrations. Together with in vitro studies, few in vivo studies have examined the capacity of these bioactive compounds to modulate the expression of miRNA. Results from these dietary interventions studies are physiologically relevant since they integrate the metabolism of polyphenols following their absorption. Under these conditions, the cellular response regarding miRNA regulation is observed in the presence of circulating metabolites at the nutritionally achievable concentrations. Highlighting the ability of polyphenols to modulate the expression of miRNAs in a nutritional context demonstrates the interest of this regulation in understanding the molecular mechanisms that govern the biological effects of polyphenols. Still, the effect of polyphenols on miRNA expression in human intervention studies remains unexplored to this day.

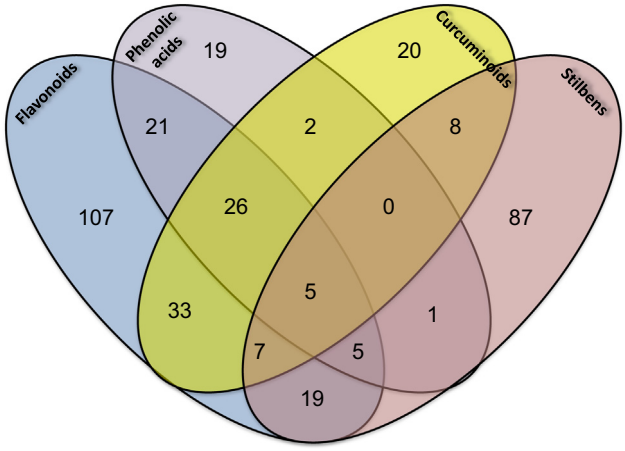

Fig. 3. Venn diagram of differentially expressed miRNAs identified for flavonoids, phenolic acids, curcuminoids, and stilbenes.

Taken together, the data generated from these studies reveal the capacity of dietary polyphenols to modulate expression of miRNA and provide insights of new mechanisms of action of these bioactive compounds underlying their beneficial health properties. Consequently, in future studies aiming to identify the mechanisms underlying biological effects of polyphenols, their impact on the expression of miRNAs should be taken into account together with their effect on cell signaling pathways, transcription factor activity,

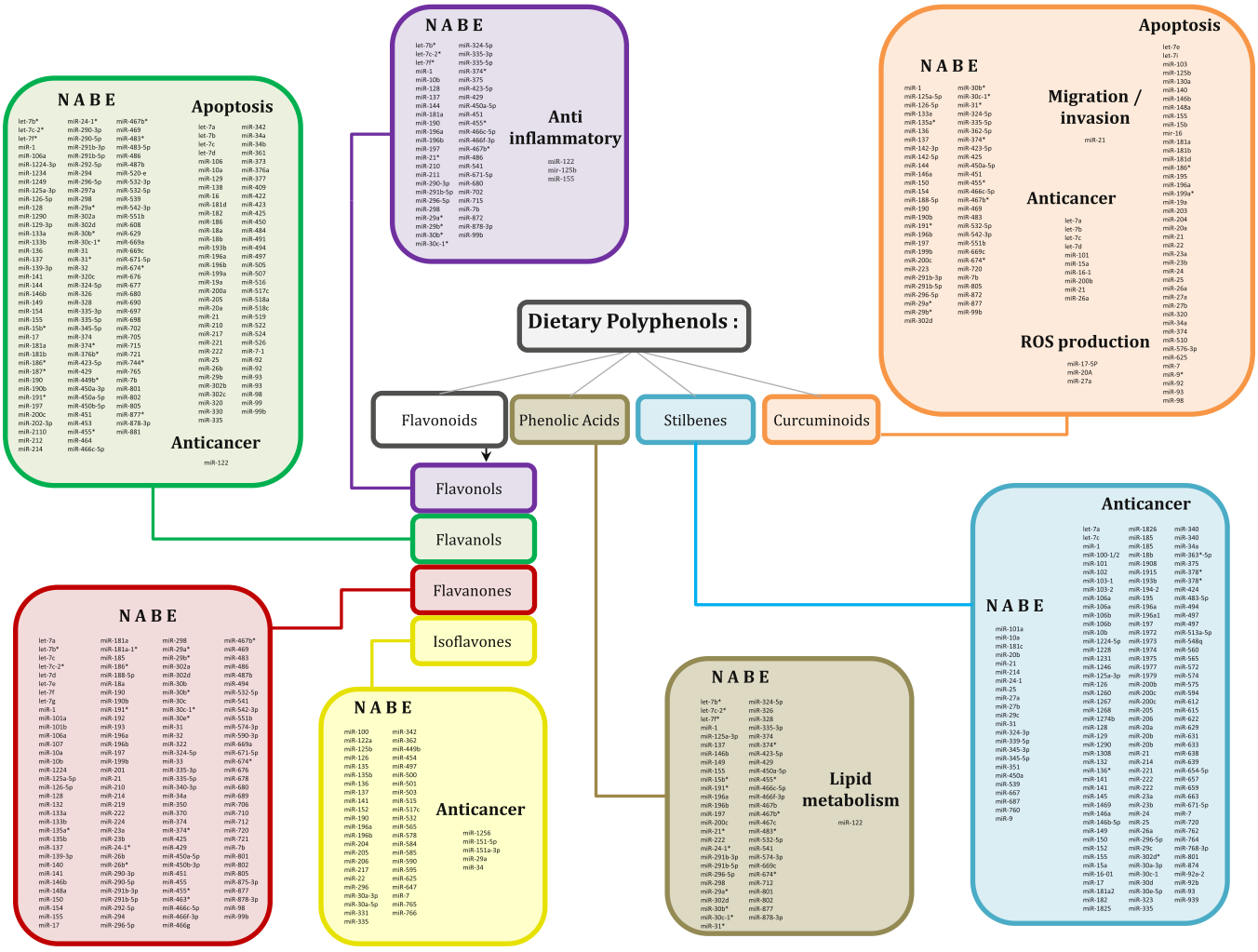

Fig. 4. Summary of microRNAs modulated by polyphenols and associated processes. NABE: No Associated Biological Effect.

and expression of genes and proteins. However, we strongly recommend, for in vitro studies aiming to study the impact of dietary polyphenols on the expression of miRNA, the use of primary cells rather than cell lines, circulating metabolites of polyphenols, and appropriate physiologically relevant concentrations of these compounds.

References

[1] Slavin, J. L.; Lloyd, B. Health benefits of fruits and vegetables. *Adv. Nutr.* **3:**506–516; 2012.

[2] Perez-Jimenez, J.; Fezeu, L.; Touvier, M.; Arnault, N.; Manach, C.; Hercberg, S.; Galan, P.; Scalbert, A. Dietary intake of 337 polyphenols in French adults. *Am. J. Clin. Nutr.* **93:**1220–1228; 2011.

[3] Cassidy, A.; O'Reilly, E. J.; Kay, C.; Sampson, L.; Franz, M.; Forman, J. P.; Curhan, G.; Rimm, E. B. Habitual intake of flavonoid subclasses and incident hypertension in adults. *Am. J. Clin. Nutr.* **93:**338–347; 2011.

[4] Clifford, M. N.; Brown, J. E. Dietary flavonoids and health—broadening the perspective. In: Andersen, O. M., Markham, K. R., editors. *Flavonoids: chemistry, biochemistry and applications*. Boca Raton: CRC Press; 2006.

[5] Manach, C.; Williamson, G.; Morand, C.; Scalbert, A.; Remesy, C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am. J. Clin. Nutr.* **81:**230 S-242 S; 2005.

[6] Peterson, J. J.; Dwyer, J. T.; Jacques, P. F.; McCullough, M. L. Associations between flavonoids and cardiovascular disease incidence or mortality in European and US populations. *Nutr. Rev.* **70:**491–508; 2012.

[7] Mink, P. J.; Scrafford, C. G.; Barraj, L. M.; Harnack, L.; Hong, C. P.; Nettleton, J. A.; Jacobs Jr. D. R. Flavonoid intake and cardiovascular disease mortality: a prospective study in postmenopausal women. *Am. J. Clin. Nutr.* **85:**895–909; 2007.

[8] Letenneur, L.; Proust-Lima, C.; Le Gouge, A.; Dartigues, J. F.; Barberger-Gateau, P. Flavonoid intake and cognitive decline over a 10-year period. *Am. J. Epidemiol.* **165:**1364–1371; 2007.

[9] Miller, P. E.; Snyder, D. C. Phytochemicals and cancer risk: a review of the epidemiological evidence. *Nutr. Clin. Pract.* **27:**599–612; 2012.

[10] van Dam, R. M.; Naidoo, N.; Landberg, R. Dietary flavonoids and the development of type 2 diabetes and cardiovascular diseases: review of recent findings. *Curr. Opin. Lipidol.* **24:**25–33; 2013.

[11] Habauzit, V.; Morand, C. Evidence for a protective effect of polyphenols-containing foods on cardiovascular health: an update for clinicians. *Ther. Adv. Chronic Dis* **3:**87–106; 2012.

[12] Del Rio, D.; Rodriguez-Mateos, A.; Spencer, J.P.; Tognolini, M.; Borges, G.; Crozier, A. Dietary (poly)phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. Antioxid. Redox Signal.; 2012.

[13] Williams, R. J.; Spencer, J. P. Flavonoids, cognition, and dementia: actions, mechanisms, and potential therapeutic utility for Alzheimer disease. *Free Radic. Biol. Med.* **52:**35–45; 2012.

[14] Cimino, S.; Sortino, G.; Favilla, V.; Castelli, T.; Madonia, M.; Sansalone, S.; Russo, G. I.; Morgia, G. Polyphenols: key issues involved in chemoprevention of prostate cancer. *Oxid. Med. Cell Longev* **2012:**632959; 2012.

[15] Fraga, C. G.; Galleano, M.; Verstraeten, S. V.; Oteiza, P. I. Basic biochemical mechanisms behind the health benefits of polyphenols. *Mol. Aspects Med.* **31:**435–445; 2010.

[16] Auclair, S.; Milenkovic, D.; Besson, C.; Chauvet, S.; Gueux, E.; Morand, C.; Mazur, A.; Scalbert, A. Catechin reduces atherosclerotic lesion development in apo E-deficient mice: a transcriptomic study. *Atherosclerosis* **204:**e21–e27; 2009.

[17] Mauray, A.; Felgines, C.; Morand, C.; Mazur, A.; Scalbert, A.; Milenkovic, D. Bilberry anthocyanin-rich extract alters expression of genes related to atherosclerosis development in aorta of apo E-deficient mice. *Nutr. Metab. Cardiovasc. Dis.* **22:**72–80; 2012.

[18] Chanet, A.; Milenkovic, D.; Deval, C.; Potier, M.; Constans, J.; Mazur, A.; Bennetau-Pelissero, C.; Morand, C.; Berard, A. M. Naringin, the major grapefruit flavonoid, specifically affects atherosclerosis development in diet-induced hypercholesterolemia in mice. *J. Nutr. Biochem.* **23:**469–477; 2012.

[19] Coban, D.; Milenkovic, D.; Chanet, A.; Khallou-Laschet, J.; Sabbe, L.; Palagani, A.; Vanden Berghe, W.; Mazur, A.; Morand, C. Dietary curcumin inhibits atherosclerosis by affecting the expression of genes involved in leukocyte adhesion and transendothelial migration. *Mol. Nutr. Food Res.* **56:**1270–1281; 2012.

[20] Milenkovic, D.; Deval, C.; Dubray, C.; Mazur, A.; Morand, C. Hesperidin displays relevant role in the nutrigenomic effect of orange juice on blood leukocytes in human volunteers: a randomized controlled cross-over study. *PLoS One* **6:**e26669; 2011.

[21] Bartel, D. P. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* **116:**281–297; 2004.

[22] Carthew, R. W.; Sontheimer, E. J. Origins and mechanisms of miRNAs and siRNAs. *Cell* **136:**642–655; 2009.

[23] Li, L.; Xu, J.; Yang, D.; Tan, X.; Wang, H. Computational approaches for microRNA studies: a review. Mamm. Genome **21:**1-12.

[24] Esquela-Kerscher, A.; Slack, F. J. Oncomirs—microRNAs with a role in cancer. *Nat. Rev. Cancer* **6:**259–269; 2006.

[25] Miska, E. A. How microRNAs control cell division, differentiation and death. *Curr. Opin. Genet. Dev* **15:**563–568; 2005.

[26] Wang, Y.; Lee, C. G. MicroRNA and cancer—focus on apoptosis. *J. Cell. Mol. Med.* **13:**12–23; 2009.

[27] Dyrskjot, L.; Ostenfeld, M. S.; Bramsen, J. B.; Silahtaroglu, A. N.; Lamy, P.; Ramanathan, R.; Fristrup, N.; Jensen, J. L.; Andersen, C. L.; Zieger, K.; Kauppinen, S.; Ulhoi, B. P.; Kjems, J.; Borre, M.; Orntoft, T. F. Genomic profiling of microRNAs in bladder cancer: miR-129 is associated with poor outcome and promotes cell death in vitro. *Cancer Res.* **69:**4851–4860; 2009.

[28] Eisenberg, I.; Alexander, M. S.; Kunkel, L. M. miRNAS in normal and diseased skeletal muscle. *J. Cell. Mol. Med.* **13:**2–11; 2009.

[29] Matkovich, S. J.; Van Booven, D. J.; Youker, K. A.; Torre-Amione, G.; Diwan, A.; Eschenbacher, W. H.; Dorn, L. E.; Watson, M. A.; Margulies, K. B.; Dorn 2nd G. W. Reciprocal regulation of myocardial microRNAs and messenger RNA in human cardiomyopathy and reversal of the microRNA signature by biomechanical support. *Circulation* **119:**1263–1271; 2009.

[30] Vickers, K. C.; Remaley, A. T. MicroRNAs in atherosclerosis and lipoprotein metabolism. *Curr. Opin. Endocrinol. Diabetes Obes* **17:**150–155; 2010.

[31] Bonauer, A.; Boon, R.A.; Dimmeler, S. Vascular microRNAs. Curr. Drug Targets **11:**943-949.

[32] Drummond, M. J.; Glynn, E. L.; Fry, C. S.; Dhanani, S.; Volpi, E.; Rasmussen, B. B. Essential amino acids increase microRNA-499, -208b, and -23a and down-regulate myostatin and myocyte enhancer factor 2C mRNA expression in human skeletal muscle. *J. Nutr.* **139:**2279–2284; 2009.

[33] Davis, C. D.; Ross, S. A. Evidence for dietary regulation of microRNA expression in cancer cells. *Nutr. Rev.* **66:**477–482; 2008.

[34] Davidson, L. A.; Wang, N.; Shah, M. S.; Lupton, J. R.; Ivanov, I.; Chapkin, R. S. n-3 Polyunsaturated fatty acids modulate carcinogen-directed non-coding microRNA signatures in rat colon. *Carcinogenesis* **30:**2077–2084; 2009.

[35] Izzotti, A.; Cartiglia, C.; Steele, V. E.; De Flora, S. MicroRNAs as targets for dietary and pharmacological inhibitors of mutagenesis and carcinogenesis. *Mutat. Res.* **751:**287–303; 2012.

[36] Kanwar, J.; Taskeen, M.; Mohammad, I.; Huo, C.; Chan, T. H.; Dou, Q. P. Recent advances on tea polyphenols. *Front. Biosci. (Elite Ed.)* **4:**111–131; 2012.

[37] Widlansky, M. E.; Hamburg, N. M.; Anter, E.; Holbrook, M.; Kahn, D. F.; Elliott, J. G.; Keaney Jr. J. F.; Vita, J. A. Acute EGCG supplementation reverses endothelial dysfunction in patients with coronary artery disease. *J. Am. Coll. Nutr.* **26:**95–102; 2007.

[38] Zheng, X. X.; Xu, Y. L.; Li, S. H.; Liu, X. X.; Hui, R.; Huang, X. H. Green tea intake lowers fasting serum total and LDL cholesterol in adults: a meta-analysis of 14 randomized controlled trials. *Am. J. Clin. Nutr.* **94:**601–610; 2011.

[39] Chakrabarti, M.; Khandkar, M.; Banik, N. L.; Ray, S. K. Alterations in expression of specific microRNAs by combination of 4-HPR and EGCG inhibited growth of human malignant neuroblastoma cells. *Brain Res* **1454:**1–13; 2012.

[40] Wang, H.; Bian, S.; Yang, C. S. Green tea polyphenol EGCG suppresses lung cancer cell growth through upregulating miR-210 expression caused by stabilizing HIF-1alpha. *Carcinogenesis* **32:**1881–1889; 2011.

[41] Tsang, W. P.; Kwok, T. T. Epigallocatechin gallate up-regulation of miR-16 and induction of apoptosis in human cancer cells. *J. Nutr. Biochem.* **21:**140–146; 2010.

[42] Long, L. H.; Hoi, A.; Halliwell, B. Instability of, and generation of hydrogen peroxide by, phenolic compounds in cell culture media. *Arch. Biochem. Biophys.* **501:**162–169; 2010.

[43] Siddiqui, I. A.; Asim, M.; Hafeez, B. B.; Adhami, V. M.; Tarapore, R. S.; Mukhtar, H. Green tea polyphenol EGCG blunts androgen receptor function in prostate cancer. *FASEB J* **25:**1198–1207; 2011.

[44] Hooper, L.; Kay, C.; Abdelhamid, A.; Kroon, P. A.; Cohn, J. S.; Rimm, E. B.; Cassidy, A. Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: a systematic review and meta-analysis of randomized trials. *Am. J. Clin. Nutr.* **95:**740–751; 2012.

[45] Milenkovic, D.; Deval, C.; Gouranton, E.; Landrier, J. F.; Scalbert, A.; Morand, C.; Mazur, A. Modulation of miRNA expression by dietary polyphenols in apoE deficient mice: a new mechanism of the action of polyphenols. *PLoS One* **7:**e29837; 2012.

[46] Russo, M.; Spagnuolo, C.; Tedesco, I.; Bilotto, S.; Russo, G. L. The flavonoid quercetin in disease prevention and therapy: facts and fancies. *Biochem. Pharmacol.* **83:**6–15; 2012.

[47] Dajas, F. Life or death: neuroprotective and anticancer effects of quercetin. *J. Ethnopharmacol.* **143:**383–396; 2012.

[48] Boesch-Saadatmandi, C.; Loboda, A.; Wagner, A. E.; Stachurska, A.; Jozkowicz, A.; Dulak, J.; Doring, F.; Wolffram, S.; Rimbach, G. Effect of quercetin and its metabolites isorhamnetin and quercetin-3-glucuronide on inflammatory gene expression: role of miR-155. *J. Nutr. Biochem.* **22:**293–299; 2011.

[49] Boesch-Saadatmandi, C.; Wagner, A. E.; Wolffram, S.; Rimbach, G. Effect of quercetin on inflammatory gene expression in mice liver in vivo—role of redox factor 1, miRNA-122 and miRNA-125b. *Pharmacol. Res* **65:**523–530; 2012.

[50] Lam, T. K.; Shao, S.; Zhao, Y.; Marincola, F.; Pesatori, A.; Bertazzi, P. A.; Caporaso, N. E.; Wang, E.; Landi, M. T. Influence of quercetin-rich food intake on microRNA expression in lung cancer tissues. *Cancer Epidemiol. Biomarkers Prev* **21:**2176–2184; 2012.

[51] Chanet, A.; Milenkovic, D.; Manach, C.; Mazur, A.; Morand, C. Citrus flavanones: what is their role in cardiovascular protection? *J. Agric. Food Chem.* **60:**8809–8822; 2012.

[52] Pilsakova, L.; Riecansky, I.; Jagla, F. The physiological actions of isoflavone phytoestrogens. *Physiol. Res.* **59:**651–664; 2010.

[53] Li, Y.; Kong, D.; Bao, B.; Ahmad, A.; Sarkar, F. H. Induction of cancer cell death by isoflavone: the role of multiple signaling pathways. *Nutrients* **3:**877–896; 2011.
[54] Chiyomaru, T.; Yamamura, S.; Zaman, M. S.; Majid, S.; Deng, G.; Shahryari, V.; Saini, S.; Hirata, H.; Ueno, K.; Chang, I.; Tanaka, Y.; Tabatabai, Z. L.; Enokida, H.; Nakagawa, M.; Dahiya, R. Genistein suppresses prostate cancer growth through inhibition of oncogenic microRNA-151. *PLoS One* **7:**e43812; 2012.
[55] Parker, L. P.; Taylor, D. D.; Kesterson, J.; Metzinger, D. S.; Gercel-Taylor, C. Modulation of microRNA associated with ovarian cancer cells by genistein. *Eur. J. Gynaecol. Oncol.* **30:**616–621; 2009.
[56] Noratto, G. D.; Angel-Morales, G.; Talcott, S. T.; Mertens-Talcott, S. U. Polyphenolics from acai (Euterpe oleracea Mart.) and red muscadine grape (Vitis rotundifolia) protect human umbilical vascular endothelial cells (HUVEC) from glucose- and lipopolysaccharide (LPS)-induced inflammation and target microRNA-126. *J. Agric. Food Chem* **59:**7999–8012; 2011.
[57] Banerjee, N.; Talcott, S.; Safe, S.; Mertens-Talcott, S. U. Cytotoxicity of pomegranate polyphenolics in breast cancer cells in vitro and vivo: potential role of miRNA-27a and miRNA-155 in cell survival and inflammation. *Breast Cancer Res. Treat* **136:**21–34; 2012.
[58] Kresty, L. A.; Clarke, J.; Ezell, K.; Exum, A.; Howell, A. B.; Guettouche, T. MicroRNA alterations in Barrett's esophagus, esophageal adenocarcinoma, and esophageal adenocarcinoma cell lines following cranberry extract treatment: insights for chemoprevention. *J. Carcinog* **10:**34; 2011.
[59] Fix, L. N.; Shah, M.; Efferth, T.; Farwell, M. A.; Zhang, B. MicroRNA expression profile of MCF-7 human breast cancer cells and the effect of green tea polyphenon-60. *Cancer Genomics Proteomics* **7:**261–277; 2010.
[60] Tunca, B.; Tezcan, G.; Cecener, G.; Egeli, U.; Ak, S.; Malyer, H.; Tumen, G.; Bilir, A. Olea europaea leaf extract alters microRNA expression in human glioblastoma cells. *J. Cancer Res. Clin. Oncol.* **138:**1831–1844; 2012.
[61] Noratto, G. D.; Kim, Y.; Talcott, S. T.; Mertens-Talcott, S. U. Flavonol-rich fractions of yaupon holly leaves (Ilex vomitoria, Aquifoliaceae) induce microRNA-146a and have anti-inflammatory and chemopreventive effects in intestinal myofibroblast CCD-18Co cells. *Fitoterapia* **82:**557–569; 2011.
[62] Zhu, M.; Wang, N.; Tsao, S. W.; Yuen, M. F.; Feng, Y.; Wan, T. S.; Man, K. Up-regulation of microRNAs, miR21 and miR23a in human liver cancer cells treated with Coptidis rhizoma aqueous extract. *Exp. Ther. Med* **2:**27–32; 2011.
[63] Joven, J.; Espinel, E.; Rull, A.; Aragones, G.; Rodriguez-Gallego, E.; Camps, J.; Micol, V.; Herranz-Lopez, M.; Menendez, J. A.; Borras, I.; Segura-Carretero, A.; Alonso-Villaverde, C.; Beltran-Debon, R. Plant-derived polyphenols regulate expression of miRNA paralogs miR-103/107 and miR-122 and prevent diet-induced fatty liver disease in hyperlipidemic mice. *Biochim. Biophys. Acta* **1820:**894–899; 2012.
[64] Murase, T.; Misawa, K.; Minegishi, Y.; Aoki, M.; Ominami, H.; Suzuki, Y.; Shibuya, Y.; Hase, T. Coffee polyphenols suppress diet-induced body fat accumulation by downregulating SREBP-1c and related molecules in C57BL/6J mice. *Am. J. Physiol. Endocrinol. Metab.* **300:**E122–E133; 2011.
[65] Wen, X. Y.; Wu, S. Y.; Li, Z. Q.; Liu, Z. Q.; Zhang, J. J.; Wang, G. F.; Jiang, Z. H.; Wu, S. G. Ellagitannin (BJA3121), an anti-proliferative natural polyphenol compound, can regulate the expression of MiRNAs in HepG2 cancer cells. *Phytother. Res.* **23:**778–784; 2009.
[66] Esatbeyoglu, T.; Huebbe, P.; Ernst, I. M.; Chin, D.; Wagner, A. E.; Rimbach, G. Curcumin—from molecule to biological function. *Angew. Chem. Int. Ed. Engl.* **51:**5308–5332; 2012.
[67] Strimpakos, A. S.; Sharma, R. A. Curcumin: preventive and therapeutic properties in laboratory studies and clinical trials. *Antioxid. Redox Signal.* **10:**511–545; 2008.
[68] Zhou, H.; Beevers, C. S.; Huang, S. The targets of curcumin. *Curr. Drug Targets* **12:**332–347; 2011.
[69] Gandhy, S. U.; Kim, K.; Larsen, L.; Rosengren, R. J.; Safe, S. Curcumin and synthetic analogs induce reactive oxygen species and decreases specificity protein (Sp) transcription factors by targeting microRNAs. *BMC Cancer* **12:**564; 2012.
[70] Mudduluru, G.; George-William, J. N.; Muppala, S.; Asangani, I. A.; Kumarswamy, R.; Nelson, L. D.; Allgayer, H. Curcumin regulates miR-21 expression and inhibits invasion and metastasis in colorectal cancer. *Biosci. Rep.* **31:**185–197; 2011.
[71] Saini, S.; Arora, S.; Majid, S.; Shahryari, V.; Chen, Y.; Deng, G.; Yamamura, S.; Ueno, K.; Dahiya, R. Curcumin modulates microRNA-203-mediated regulation of the Src-Akt axis in bladder cancer. *Cancer Prev. Res. (Phila.)* **4:**1698–1709; 2011.
[72] Zhang, J.; Du, Y.; Wu, C.; Ren, X.; Ti, X.; Shi, J.; Zhao, F.; Yin, H. Curcumin promotes apoptosis in human lung adenocarcinoma cells through miR-186* signaling pathway. *Oncol. Rep.* ***24:***1217–1223; 2010.
[73] Gao, S. M.; Yang, J. J.; Chen, C. Q.; Chen, J. J.; Ye, L. P.; Wang, L. Y.; Wu, J. B.; Xing, C. Y.; Yu, K. Pure curcumin decreases the expression of WT1 by upregulation of miR-15a and miR-16-1 in leukemic cells. *J. Exp. Clin. Cancer Res.* **31:**27; 2012.
[74] Sun, M.; Estrov, Z.; Ji, Y.; Coombes, K. R.; Harris, D. H.; Kurzrock, R. Curcumin (diferuloylmethane) alters the expression profiles of microRNAs in human pancreatic cancer cells. *Mol. Cancer Ther* **7:**464–473; 2008.
[75] Yu, W.; Fu, Y. C.; Wang, W. Cellular and molecular effects of resveratrol in health and disease. *J. Cell Biochem.* **113:**752–759; 2012.
[76] Li, H.; Xia, N.; Forstermann, U. Cardiovascular effects and molecular targets of resveratrol. *Nitric Oxide* **26:**102–110; 2012.
[77] Han, Z.; Yang, Q.; Liu, B.; Wu, J.; Li, Y.; Yang, C.; Jiang, Y. MicroRNA-622 functions as a tumor suppressor by targeting K-Ras and enhancing the anticarcinogenic effect of resveratrol. *Carcinogenesis* **33:**131–139; 2012.
[78] Tili, E.; Michaille, J. J.; Adair, B.; Alder, H.; Limagne, E.; Taccioli, C.; Ferracin, M.; Delmas, D.; Latruffe, N.; Croce, C. M. Resveratrol decreases the levels of miR-155 by upregulating miR-663, a microRNA targeting JunB and JunD. *Carcinogenesis* **31:**1561–1566; 2010.
[79] Dhar, S.; Hicks, C.; Levenson, A. S. Resveratrol and prostate cancer: promising role for microRNAs. *Mol. Nutr. Food Res.* **55:**1219–1229; 2011.
[80] Sheth, S.; Jajoo, S.; Kaur, T.; Mukherjea, D.; Sheehan, K.; Rybak, L. P.; Ramkumar, V. Resveratrol reduces prostate cancer growth and metastasis by inhibiting the Akt/MicroRNA-21 pathway. *PLoS One* **7:**e51655; 2012.
[81] Tili, E.; Michaille, J. J.; Alder, H.; Volinia, S.; Delmas, D.; Latruffe, N.; Croce, C. M. Resveratrol modulates the levels of microRNAs targeting genes encoding tumor-suppressors and effectors of TGFbeta signaling pathway in SW480 cells. *Biochem. Pharmacol.* **80:**2057–2065; 2010.
[82] Mukhopadhyay, P.; Mukherjee, S.; Ahsan, K.; Bagchi, A.; Pacher, P.; Das, D. K. Restoration of altered microRNA expression in the ischemic heart with resveratrol. *PLoS One* **5:**e15705; 2010.
[83] Krol, J.; Loedige, I.; Filipowicz, W. The widespread regulation of microRNA biogenesis, function and decay. *Nat. Rev. Genet.* **11:**597–610; 2010.
[84] Breving, K.; Esquela-Kerscher, A. The complexities of microRNA regulation: mirandering around the rules. *Int. J. Biochem. Cell Biol.* **42:**1316–1329; 2010.
[85] Shehzad, A.; Lee, Y. S. Molecular mechanisms of curcumin action: signal transduction. *Biofactors* **39:**27–36; 2013.
[86] George, J.; Singh, M.; Srivastava, A. K.; Bhui, K.; Roy, P.; Chaturvedi, P. K.; Shukla, Y. Resveratrol and black tea polyphenol combination synergistically suppress mouse skin tumors growth by inhibition of activated MAPKs and p53. *PLoS One* **6:**e23395; 2011.
[87] Gonzalez-Sarrias, A.; Espin, J. C.; Tomas-Barberan, F. A.; Garcia-Conesa, M. T. Gene expression, cell cycle arrest and MAPK signalling regulation in Caco-2 cells exposed to ellagic acid and its metabolites, urolithins. *Mol. Nutr. Food Res.* **53:**686–698; 2009.
[88] Halliwell, B. Are polyphenols antioxidants or pro-oxidants? What do we learn from cell culture and in vivo studies? *Arch. Biochem. Biophys* **476:**107–112; 2008.
[89] Spencer, J. P. The impact of fruit flavonoids on memory and cognition. *Br. J. Nutr.* **104(Suppl. 3):**S40–47; 2010.
[90] Fraga, C. G.; Oteiza, P. I. Dietary flavonoids: role of (-)-epicatechin and related procyanidins in cell signaling. *Free Radic. Biol. Med.* **51:**813–823; 2011.
[91] Kroon, P. A.; Clifford, M. N.; Crozier, A.; Day, A. J.; Donovan, J. L.; Manach, C.; Williamson, G. How should we assess the effects of exposure to dietary polyphenols in vitro? *Am. J. Clin. Nutr.* **80:**15–21; 2004.