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Chapter

The Impact of Dietary Compounds in Functional Foods on MicroRNAs Expression

Wittaya Chaiwangyen

Abstract

MicroRNAs (miRNAs) are a class of non-coding endogenous RNA molecules that are involved in post-transcriptional gene silencing via binding to their target messenger RNA, leading to mRNA degradation or translational repression. MicroRNAs can be modulated by several factors including hormones, transcription factors, and dietary compounds. These biologically active compounds have positive impact on the progression of human pathology including non-communicable diseases, which indicating that administration of diet may have potential as therapeutic agents in modulating the risk of chronic diseases. Interestingly, evidence emerging in recent years suggests that dietary miRNAs can be absorbed in human circulation, modulated human gene expression and biological functions. The exploitation of the miRNA functioning within different origins, cellular miRNAs and dietary miRNAs will help us to understand the molecular machinery as well as the regulatory mechanisms involved in fundamentally important biological processes. Therefore, this knowledge may be applied of natural bioactive compounds in preventive or therapeutic approaches.

Keywords: functional foods, microRNAs, dietary microRNAs, chronic diseases, non-communicable diseases

1. Origin, biogenesis and functions of microRNAs

MicroRNAs or miRNAs are a class of small non-coding RNA approximately 21–25 nucleotides that modulate on gene expression post-transcriptionally via binding to the 3′ untranslated region (3′-UTR) of the target messenger RNA (mRNA), resulting in mRNA degradation or translational repression. The first miRNA, lin-4, was discovered by Ambro and his research group in 1993 and it was found to be related with larva development in *Caenorhabditis elegans* [1]. Up to date, almost 2000 miRNAs have been identified in humans (http://www.miRbase.org – 7.3.2019) [1]. It has been estimated that 1–4% of human genes expression can be regulated by miRNAs, which is the largest of genomic regulator [2]. In mammals, miRNAs have been associated with various cellular pathways with the regulation of cell differentiation, cell cycle, proliferation, apoptosis, hematopoiesis, and other cellular functions. Recent studies have highlighted the importance of mRNA regulation mechanism by validation and differential miRNA expression in a variety of human pathological conditions, including chronic diseases.

miRNAs are normally transcribed by RNA polymerase II from miRNA genes. This transcription leads to generate a primary miRNA transcript (pri-miRNA). Then, pri-miRNA is further cleaved by a microprocessor complex, which consists of Drosha, the double-stranded RNase III enzyme and DiGeorge syndrome critical region 8 (DGCR8), important cofactor, into a hairpin structure precursor miRNA (pre-miRNA) in the nucleus (**Figure 1**). The double strand pre-miRNAs with 70 nucleotides are then exported to the cytoplasm by the process of nuclear export factor exportin-5. The pre-miRNA is then processed by RNase III, Dicer, thereby generating a mature miRNA:miRNA duplex approximately 22 nucleotides in length and without a hairpin structure. The helicase enzyme cleaves miRNA duplexes into single-stranded miRNAs and incorporated into the Argonaute (AGO), TRBP and PACT proteins to form the RNA-induced silencing complex (RISC). Usually, other single strand called passenger strand or the star (*) strand will be degraded, while single strand mature miRNA is able to bind with its target mRNA and mediating translational inhibition or mRNA degradation, along with their sequence complementarity to the target [1, 3]. In plants, target mRNA will be degraded if miRNA has perfect or near-perfect complementarity to its target. In contrast to mammal, miRNAs bind to partially complementary sites in the 3′-UTRs of target mRNA, which leading to translational repression [4]. the target mRNA is either blocked (imperfect complementary) or degraded (perfect complementary) of the ribosomal translation, which sequentially impacts the cellular functions.

Phytochemicals are major plant-derived compounds that naturally found in vegetables, fruits, medicinal plants or other plants with medicinal properties including antioxidant, anti-diabetic, anti-inflammatory, antimicrobial, antidepressant, anticancer and prevention in other chronic non-communicable diseases [5–7]. Phenolic and flavonoid compounds are the most important group of bioactive compounds and second metabolites in plants which comprise of essential molecules

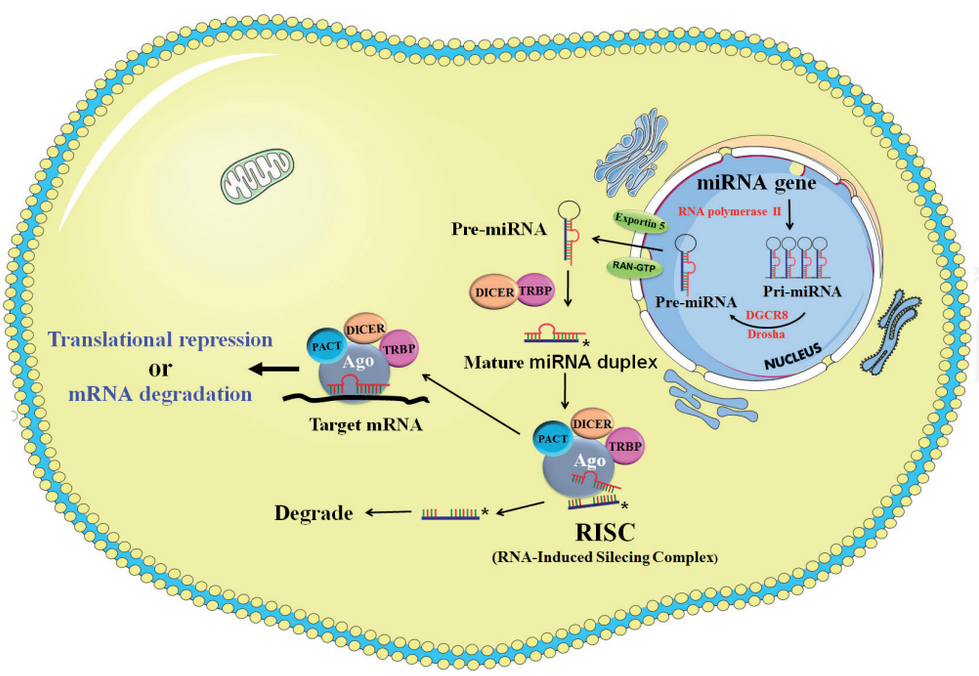

Figure 1.
miRNA biogenesis. miRNA gene is transcribed by RNA polymerase II and then forming the primary miRNA transcript (pri-miRNA), which is further cleaved by the Drosha/DGCR8 complex to generate the precursor miRNA (pre-miRNA). Pre-miRNA is then exported into the cytoplasm by exportin 5/RAN-GTP and further processed by dicer to create the mature miRNA, which is loaded into RISC, which contains AGO, PACT and TRBP proteins. Mature miRNA that binding to its target mRNA by perfect complementary binding and resulting in gene suppression by mRNA degradation. The partially complementary binding of miRNA and its target mRNA, which in turn inhibit the protein translation.

of human diet [6, 8]. It has been shown that bioactive compounds can modulate the endogenous miRNAs expression [1, 9–12]. Recently, some studies have revealed that plant-derived miRNAs (dietary miRNAs) as new bioactive compounds in plants can affect the synthesis of endogenous miRNAs [13–15]. Strikingly, miRNAs do not function only their origins but they are able to regulate the gene expression in cross-kingdom. Therefore, bioactive compounds present in functional foods are potentially regulate endogenous miRNAs expression.

2. Dietary compounds and endogenous miRNAs

Extensive studies have been performed to understand the molecular mechanism of bioactive compounds with a positive effect on chronic diseases or non-communicable diseases such as arthritis, cancer, cardiovascular diseases, diabetes and obesity [1, 16]. Emerging evidences confirm that alteration of endogenous miRNAs expression can be influenced by bioactive compounds in functional foods [16, 17] (**Figure 2** and **Table 1**).

2.1 Acetyl-11-keto-β-boswellic acid

3-acetyl-11-keto- β -boswellic acid (AKBA) is pentacyclic triterpene acids that mainly found in *Boswellia serrata* and it has been shown in medicinal properties for chronic diseases including anti-tumor, anti-inflammation, antioxidant, asthma, diabetes, atherosclerosis and analgesic [18–20]. AKBA showed the reduction of

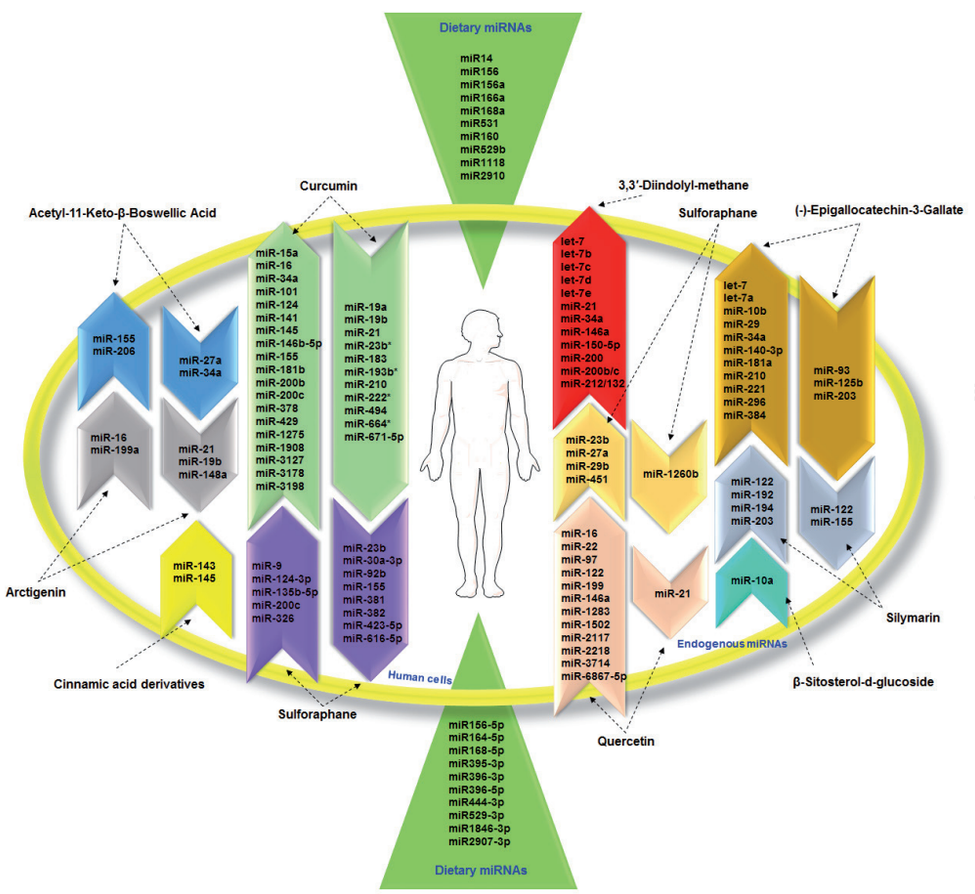

Figure 2.
Influences of bioactive compounds and dietary miRNAs on human non-communicable diseases. Ascending arrows represent up-regulated miRNAs and descending arrows represent down-regulated miRNAs by bioactive compounds. The green triangles show the positive impact of dietary miRNAs on human health.

Dietary compound	miRNA expression		Target of miRNA	Diseases	References
	Up-regulation	Down-regulation			
Acetyl-11-Keto-β-Boswellic Acid		miR-27a miR-34a	Unknown	Colorectal cancer	[23]
	miR-155		SOCS-1	Neuroinflammation	[21]
	miR-206		ER-α	Breast cancer	[22]
Arctigenin	miR-16 miR-199a		Unknown	Neuroinflammation	[28]
		miR-21 miR-19b miR-148a	Unknown	Prostate cancer	[29]
Cinnamic acid derivatives	miR-143		MAPK/ Erk5	Colon cancer	[31]
	miR-145		Unknown	Gastric cancer	[33]
Curcumin	miR-15a, miR-16, miR-34a, miR-146b-5p miR-181b	miR-19a miR-19b	Unknown	Breast cancer	[38]
	miR-101, miR-200b, miR-200c, miR-141 miR-429	miR-21	Unknown	Colorectal cancer	[39, 40]
		miR-21		Gastric cancer	[41]
	miR-145 miR-1275 miR-1908 miR-3127 miR-3178 miR-3198	miR-23b*, miR-183 miR-193b* miR-210 miR-222* miR-494 miR-664* miR-671-5p	Oct4	Prostate cancer	[42]
	miR-181b		CXCL1 CXCL2	Breast cancer	[43]
	miR-378		p38	glioblastoma	[44]
	miR-124 miR-155		Unknown	Neurodegenerative disorder	[45]
3,3′-Diindolyl-methane	let-7 miR-34a miR-150-5p		EZH2, Notch1 AR Ahr	Prostate cancer	[46]
	miR-200		FoxM1	Breast cancer	[47]
	miR-212/132 cluster miR-21		Sox4 Cdc25A	Breast cancer	[48, 49]
	let-7b, let-7c, let-7d, let-7e, and miR-200b/c		ZEB-1, E-cadherin	Pancreatic cancer	[50]
	miR-146a		Unknown	Pancreatic cancer	[51]

Dietary compound	miRNA expression		Target of miRNA	Diseases	References
	Up-regulation	Down-regulation			
(−)-Epigallocatechin-3-Gallate	miR-296		STAT3	Nasopharyngeal carcinoma	[57]
	let-7a miR34a		c-Myc	Hepatocellular carcinoma	[58]
	miR-34a	miR-93	Unknown	Prostate cancer	[59]
	miR-29 miR-210	miR-125b miR-203	Unknown	Cervical cancer	[60]
	let-7		HMGA2	Melanoma cell	[61]
	miR-384		Beclin-1	Myocardial ischemia/ reperfusion	[62]
	miR-140-3p		Unknown	Osteoarthritis	[63]
	miR-10b miR-181a miR-221		Unknown	Liver fibrosis	[64]
Genistein	miR-23b		Unknown	Breast cancer	[66]
		miR-1260b	sRRP1 Smad4	Prostate cancer	[67]
		miR-1260b	sFRP1, Dkk2, Smad4	Renal cancer	[68]
	miR-27a		Unknown	Lung cancer	[69]
	miR-29b		Unknown	Lung cancer	[70]
	miR-451		Unknown	Chronic liver disease	[72]
Quercetin	miR-200b-3p		Notch1	Pancreatic cancer	[75]
	miR-146a		EGFR	Breast cancer	[76]
	miR-16		HOXA10	Oral cancer	[77]
	miR-22		WNT1/β-catenin	Oral cancer	[78]
	miR-97 miR-298 miR-2218 miR-1502 miR-2117		Unknown	Oxidative stress in pheochromocytoma	[79]
	miR-503-5p miR-1283, miR-3714 miR-6867-5p		CCND1	Endometriosis	[80]
	miR-122	miR-21	Unknown	Liver fibrosis	[81]
	miR-199		Sert1	Hypoxia	[82]
Silymarin	miR-203		class 1 HDAC proteins and ZEB1	Lung cancer	[84]
		miR-155	Unknown	Rheumatoid arthritis	[85]
		miR-122	Unknown	Liver damage	[86]
	miR-122 miR-192 miR-194		Unknown	Liver damage	[87]
β-Sitosterol-d-glucoside	miR-10a		Unknown	Breast cancer	[89]

Dietary compound	miRNA expression		Target of miRNA	Diseases	References
	Up-regulation	Down-regulation			
Sulforaphane		miR-23b miR-92b miR-381 miR-382	Unknown	Breast cancer	[92]
		miR-616-5p	GSK3β/β-catenin	Lung cancer	[93]
	miR-135b-5p	miR-30a-3p	RASAL2 Cx43	Pancreatic cancer	[94]
	miR-200c		Unknown	Oral cancer	[96]
	miR-9 miR-326		Unknown	Gastric cancer	[97]
	miR-124-3p		STAT3	Nasopharyngeal cancer	[98]
		miR-423-5p	Unknown	Liver fibrosis	[99]
		miR-155	Unknown	Neuroinflammation	[100]

Table 1.
Summary of miRNAs bioactive compounds and miRNAs expression in human pathology.

inflammatory miRNA expression, miR-155 and increased the expression of miR-155 target gene, suppressor of cytokine signaling-1 (SOCS-1) in neuroinflammatory mice model [21]. Therefore, AKBA might be used for treatment of neuroinflammatory disorders. AKBA also induced breast cancer cell cycle arrest, apoptosis and decreased the expression of estrogen receptor alpha (ER-α) via the up-regulation of miR-206 [22]. In addition, combination of AKBA and curcumin suppressed colorectal cancer growth through the down-regulated miR-27a and miR-34a expression [23].

2.2 Arctigenin

Arctigenin (AR) is a phenylpropanoid dizbenzylbutyrolactone lignin and was first identified in *Arctium lappa* L. Several studies showed anti-inflammatory, anti-cancer, anti-viral, immune modulatory activities of AR [24–27]. The study demonstrated that AR upregulated miR-16 and miR-199a expression by decreasing upstream protein (IKKα and IKKβ) expression and inhibiting NF-κB signaling pathway activity, thereby reducing inflammatory cytokines production in neural cells [28]. The combination treatment of AR and quercetin significantly inhibited the oncogenic miRNAs expression including miR-19b, miR-21 and miR-148a in prostate cancer cells. AR and quercetin also showed anti-migration activity in prostate cancer cells [29].

2.3 Cinnamic acid derivatives

Cinnamic acid derivatives can occur naturally in plants and their structure composing of benzene ring and acrylic acid group. Several compounds of cinnamic acid derivatives have been identified including artepilin C, baccharin, drupanin, ferulic acid, curcumin, caffeic acid, p-hydroxycinnamic acid, coumaric and chlorogenic acids, etc. [30, 31]. Medicinal activities of cinnamic acid derivatives have been reported such as anti-inflammatory, anti-oxidant, anti-viral, anti-microbial, anti-diabetic, neuroprotective and anti-tumor activities [30–32]. Cinnamic acid derivatives

from propolis significantly induced colon cancer cell apoptosis through TRAIL/DR4/5 and/or FasL/Fas death-signaling pathways and via the upregulated miR-143 expression, resulting in decreased the target gene MAPK/Erk5 expression and its downstream target c-Myc [31]. Moreover, Li et al. demonstrated that cinnamic acid derivatives decreased gastric cancer cell proliferation through the up-regulation of miR-145 and down-regulation P13K/Akt signaling pathway [33]. Therefore, cinnamic acid derivatives have a potential as therapeutic agents for cancer.

2.4 Curcumin

Curcumin[(1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptane-3,5-dione] is well known as natural polyphenol and derived from the rhizome of turmeric or *Curcuma longa* Linn [34, 35]. Curcumin has been shown to possess of several medicinal properties such as anti-inflammation, antioxidant, pro-apoptosis, chemoprevention, anti-proliferation, wound healing, anti-nociception, anti-parasite, anti-malaria, anti-diabetes, neuroprotection and anti-tumor [34, 36]. Numerous studies have been focused on curcumin as a novel anti-cancer drug due to the inhibition of NF-kB, Akt/PI3K, and MAPK pathways and enhancement of p53 by curcumin, thereby inhibited several cancer cells proliferation, migration, invasion and induced apoptosis [35, 37]. Emerging data suggest that curcumin dysregulate oncogenic miRNAs and tumor suppressor miRNAs expression in various type of cancers such as lung cancer, prostate cancer, breast cancer, colorectal cancer, nasopharyngeal carcinoma, pancreatic cancer, ovarian cancer and etc. [35]. Curcumin have been shown to up-regulation of miR-15a, miR-16, miR-34a, miR-146b-5p and miR-181b and down-regulation of miR-19a and miR-19b upon treatment of several breast cancer cell lines with curcumin [38]. Curcumin but not 5-fluorouracil, upregulated the expression of miR-101, miR-200b, miR-200c, miR-141 and miR-429 and down-regulated oncogenic miR-21 in colorectal cancer cells [39, 40]. In addition, miR-21 was down-regulated in gastric cancer with curcumin treatment, resulting in inhibition of cell migration and invasion by regulation of the PTEN/PI3K/AKT pathway [41]. Lui et al. showed that curcumin up-regulated 6 miRNAs (miR-145, miR-1275, miR-1908, miR-3127, miR-3178, and miR-3198), whereas 8 miRNAs (miR-23b*, miR-183, miR-193b* miR-210, miR-222*, miR-494, miR-664*, miR-671-5p) were down-regulated when treated with curcumin in human prostate cancer stem cells (HuPCaSCs) [42]. Experimental confirmed of miR-145 function in HuPCaSCs revealed that miR-145 inhibited cell proliferation by targeting transcription factors Oct4 [42]. Another study also reported that miR-181b was up-regulated by curcumin and inhibited breast cancer cell proliferation, invasion and induced cell apoptosis by targeting CXCL1 and CXCL2 [43]. Inhibitory effect of curcumin on glioblastoma cell growth was observed and curcumin also up-regulated miR-378 expression and p38 was the target of miR-378 [44]. Curcumin and Pioglitazone combination have a potential as therapeutic applications for neurodegenerative disorders by increasing of miR-124 and miR-155 expression, thereby inhibiting the inflammatory cytokines TNF-α, IL-1β and IL-6 production and inflammation-associated enzymes COX-2, iNOS through inhibition of NF-κB activity in animal model [45].

2.5 3,3′-Diindolylmethane

3,3′-diindolylmethane (DIM) is a naturally active compound found in stomach, which derived from indole-3-carbinol (I3C) that present in cruciferous vegetables. DIM has been reported to regulate several miRNAs expression in cancer. Tumor suppressor miRNAs was upregulated by DIM in prostate cancer cells including let-7, miR-34a and miR-150-5p by targeting EZH2, Notch1 and AR and Ahr, respectively [46].

DIM also upregulated tumor suppressor miR-200, which led to inhibit the expression of FoxM1 in breast cancer cells [47]. miR-212/132 cluster and miR-21 were upregulated by DIM, which downregulated the expression of Sox4 and Cdc25A, respectively in breast cancer [48, 49]. Moreover, DIM upregulated let-7b, let-7c, let-7d, let-7e, and miR-200b/c expression, which led to inhibit the expression of ZEB-1, E-cadherin in pancreatic cancer cells [50]. It has been reported miR-146a was upregulated upon treated with DIM and suppressed the expression of MTA2, NF-κB, IRAK1, EGFR in pancreatic cancer cells [51].

DIM showed the modulation of miRNAs expression in other inflammatory diseases. The expression of miR-106a, miR-20b, and miR-125b-5p were increased after treatment with DIM and suppressed the expression of IRAK4 and TNF-α to limit responses to TLRs activated by LPS in acute liver failure (ALF) animal model [52]. DIM significantly upregulated miR-200c, miR-146a, miR-16, miR-93, and miR-22 in brain CD4+ T cells and inhibited the expression of cyclin E1 and B-cell lymphoma-2 in experimental autoimmune encephalomyelitis (EAE), a murine model of multiple sclerosis [53].

2.6 (−)-Epigallocatechin-3-gallate

(−)-Epigallocatechin-3-Gallate or EGCG is a major polyphenol compound in green tea (*Camellia sinensis*) and derivative of catechin [3, 16]. EGCG is a powerful antioxidant, anticancer and antiangiogenic properties, which has a potential role to influence human diseases [54–56]. EGCG suppressed nasopharyngeal carcinoma cell migration and invasion through a novel signaling axis of miR-296/STAT3 regulation [57]. Gold nanoparticles (AuNPs) have been used for drug delivery as their stability and increase drug bioavailability as well as accumulation of drug in cancer cells. EGCG-capped gold nanoparticles upregulated the tumor suppressor miRNAs, let-7a and miR34a, which consecutively their targeted gene, caspase-3 was upregulated, and c-Myc protein was decreased in hepatocellular carcinoma cells [58]. miR-34a is one of the tumor suppressor miRNAs that downregulated, whereas miR-93 is highly up-regulated in prostate cancer cells. Co-transfection of miR.34a mimic and miR.93 inhibitor along with EGCG significantly decreased androgen receptor (AR) and prostate-specific antigen (PSA) expression when compared to the co-transfection without EGCG [59]. In cervical carcinoma cells, Hela (HPV16/18+), EGCG inhibited cell growth and up-regulated miR-29 and miR-210 expression, while down-regulated the expression of miR-125b and miR-203 [60]. Up-regulation of let-7 was observed in EGCG treated melanoma cells, which led to inhibit the expression of high mobility group A2 (HMGA2) [61].

EGCG showed the protective effect against myocardial ischemia/reperfusion (I/R) injury through up-regulation of miR-384-mediated autophagy by targeting Beclin-1 via activating the PI3K/Akt signaling pathway [62]. EGCG also demonstrated the anti-arthritic effects by inhibited IL-1β-induced ADAMTS5 expression and up-regulated the expression of miR-140-3p in osteoarthritis chondrocytes [63]. EGCG treatment has potential role of preventing toxin-induced fibrosis by suppression of osteopontin expression and up-regulation of miR-10b, miR-181a and miR-221 in liver hepatocellular carcinoma cells [64].

2.7 Genistein

Genistein belongs to isoflavone family and presents in soybeans with antiangiogenic, anti-metastasis, anti-inflammatory, anti-oxidant, cell cycle arrest and induction of apoptosis effects [65]. Genistein can regulate the expression of miRNAs in several call types [65]. It has been reported that treatment of genistein up-regulated miR-23b and inhibited breast cancer cell growth [66]. Genistein also exhibited anti-tumor effect

by down-regulated miR-1260b and targeting sRRP1 and Smad4 through DNA methylation or histone modifications in prostate cancer cells [67]. The same research group reported that miR-1260b was highly expressed in renal cancer cells and miR-1260b was down-regulated in genistein treated renal cancer cells [68]. The treatment of miR-1260b inhibitor inhibited the expression of its target genes, sFRP1, Dkk2, Smad4 [68]. Treatment with genistein induced non-small lung cancer cell apoptosis, caspase-3/9 activation and inhibited cell proliferation via up-regulation of miR-27a -mediated MET signaling [69]. Co-encapsulate miR-29b with genistein in hybrid nanoparticles (GMLHN) has been studied to treat effectively in non-small lung cancer cell and GMLHN showed the anti-proliferative effect by down-regulation of phosphorylated AKT (pAKT) and phosphorylated phosphoinositide-3 kinase (p-PI3K) [70].

Genistein promoted myoblast proliferation and differentiation through down-regulated miR-222 expression, resulting in increased expression of its target genes, MyoG, MyoD, and ERα [71]. Interestingly, genistein up-regulated miR-451 expression and inhibited IL1β expression and inflammation in chronic liver disease nonalcoholic steatohepatitis (NASH) mice model [72].

2.8 Quercetin

Quercetin is bioactive flavonoids that can be found in fruits and vegetables including onion, kale, apple, many berries, citrus fruits and tea [73]. Anti-cancer, anti-inflammatory, antioxidant, anti-diabetes, anti-atherosclerosis and anti-viral effects have been reported in different in vitro studies for quercetin [74]. Several studies have focused on quercetin and miRNAs modulation for therapeutic approaches. miR-200b-3p was up-regulated in pancreatic cancer cells when treated with quercetin, resulting in inhibition of self-renewal and decrease of proliferation through Notch1 signaling pathway [75]. Quercetin significantly inhibited breast cancer cell proliferation and invasion via up-regulated miR-146a expression and targeting EGFR [76]. Quercetin inhibited cell viability, migration and invasion by up-regulated miR-16 and targeting HOXA10 in oral cancer cells [77]. In addition, quercetin decreased oral cancer cell viability and increased cell apoptosis via miR-22/WNT1/β-catenin pathway [78].

Recently, quercetin modulated 34 miRNAs expression (5 upregulated and 29 downregulated) and novel miR-97, miR-298, miR-2218, miR-1502, and miR-2117 were identified in pheochromocytoma of the rat adrenal medulla that responded for protective effect against oxidative stress through PI3K-AKT signaling pathway [79]. Treatment of quercetin inhibited proliferation of endometriosis through up-regulated miR-503-5p, miR-1283, miR-3714 and miR-6867-5p by targeting CCND1 [80]. TGFβ1 is a fibrosis inducer and quercetin significantly down-regulated miR-21 and TGFβ1 and up-regulated miR-122 in liver fibrosis [81]. Protection of cardiomyocyte against hypoxia caused insults of quercetin has been reported by up-regulation of miR-199 mediated sirt1 expression and AMPK phosphorylation [82].

2.9 Silymarin

Silymarin is a flavonolignans extracted from the milk thistle *Silybum marianum* (L.) gaernt and recent studies have demonstrated the anti-cancer, anti-inflammatory, vascularization inhibitory, antioxidant, hepatoprotective, cardioprotective and anti-metastasis activities of silymarin [83]. Several miRNAs have been implicated in the invasive potential of cancer cells. Tumor suppressor miRNA, miR-203, was up-regulated and class 1 HDAC proteins and ZEB1 were repressed with silymarin treatment, resulted in inhibition of non-small cell lung cancer migration [84]. Silibinin, the major active constituent of silymarin extract, induced apoptosis and ERβ expression, inhibited cell proliferation, and reduced pro-inflammatory cytokines expression including IL-17 and

TNF-α, through ERβ binding and down-regulated miR-155 in rheumatoid arthritis [85]. miR-122 is liver-specific miRNA and was down-regulation upon silymarin treatment in rat model for hepatoprotective and radio protective effects via increased superoxide dismutase (SOD), glutathione (GSH) and reduced lipid peroxidation (MDA) [86]. It has been reported the hepatoprotective activity of silymarin on thioacetamide-induced liver damage by restored miR-122, miR-192, and miR-194 expression levels [87].

2.10 β-Sitosterol-d-glucoside

β-Sitosterol-d-glucoside is bioactive compounds that has been isolated from *Agave angustifolia* and sweet potato [88, 89]. Pharmacological activity of β-Sitosterol-d-glucoside has been reported including immunomodulatory, anti-inflammatory, cytotoxic, and antiparasitic activities [88]. β-Sitosterol-d-glucoside exhibited cytotoxic effect in breast cancer cells by up-regulated miR-10a expression and decreased the PI3K/Akt signaling pathway [89]. Treatment of β-Sitosterol-d-glucoside can down-regulate miR-322-5p, miR-301a-3p, miR-129-5p, miR-322-3p, and miR-129-2-3p in neural stem cell and their targets are related to the regulation of proliferation [90]. Therefore, β-Sitosterol-d-glucoside could be developed for further therapeutic applications.

2.11 Sulforaphane

Sulforaphane is dietary compounds in broccoli (*Brassica oleracea*) and cruciferous plants. It has been demonstrated the capability of sulforaphane for anti-inflammatory, antiaging, antidiabetic, antioxidant, anti-tumor, hepatoprotective and cardioprotective effects [91]. Plant-derived phytochemicals including sulforaphane are potentially affected miRNAs expression. Sulforaphane inhibited breast cancer cell cycle arrest and senescence via down-regulation of miR-23b, miR-92b, miR-381 and miR-382 [92]. Anti-tumor effect of sulforaphane also reported in non-small cell lung cancer by down-regulation of miR-616-5p and targeting GSK3β/β-catenin signaling pathway [93]. Sulforaphane inhibited the progression of pancreatic cancer through down-regulated miR30a-3p with the increasing of its target, Cx43 expression and upregulated miR-135b-5p mediated RASAL2 expression [94, 95]. In addition, sulforaphane treatment significantly increased the expression of tumor suppressor miRNA, miR-200c, resulted in inhibited the cancer stemness and tumor-initiating properties in oral squamous cell carcinomas and cancer stem cells both in vitro and in vivo [96]. Anti-proliferative and apoptotic effects of sulforaphane have been reported in gastric cancer cells, which leading to alter the expression of miR-9 and miR-326 [97]. Up-regulation of miR-124-3p and inhibition of its target, STAT3 by sulforaphane treatment were observed and thereby induced apoptosis, inhibited proliferation and decreased the stemness of nasopharyngeal cancer cell [98].

Sulforaphane has potential to inhibit hepatic fibrosis by downregulating miR-423-5p in hepatic stellate cell [99]. Sulforaphane showed the protective effect in microglia-mediated neurotoxicity by inhibited LPS-induced expression of inflammatory miRNA, miR-155 [100].

3. Dietary miRNA and human gene regulation

Several evidences demonstrated the direct modulation of cellular signaling pathways by dietary compounds could decrease the risk of chronic diseases [101]. Interestingly, it has been reported that small non-coding RNA including miRNAs can be transferred across Kingdoms, for example dietary miRNAs have been found in human body fluids and these circulating miRNAs are likely to regulate human gene

expression [15, 102–107]. The uptake of plant derived miRNAs could be in the form of raw and cooked plants in capable of stability forms [107, 108]. Due to high temperature cooking process, low pH and enzymes in digestive tract as well as enzymes in blood circulation, miRNAs might be destroyed before their functions with target mRNAs [15]. Strikingly, GC base content, 2'-O-methylation on the 3′-terminal, unique nucleotide sequence of dietary miRNAs and extracellular vesicles (exosome and microvesicle) are preventive features of plant derived miRNAs in harmful conditions [109–114].

There are numerous studies to support the functional roles of dietary miRNAs in cross kingdom gene regulation. Rice miR156a and miR168a were detected in human serum and miR168a down-regulated low-density lipoprotein receptor adapter protein 1 (LDLRAP1) expression, resulted in an increase of plasma LDL cholesterol level, **Table 2** [105]. miR2910 from *Populus euphratica* was identified in human plasma and targeting Sprouty RTK Signaling Antagonist 4 (SPRY4) gene of the Janus kinase/signal transducers and activators of transcription (JAK–STAT) signaling pathway [115]. Based on the computationally predicted miRNAs from *Camptotheca acuminate,* 14 potential miRNAs were found to be regulated 152 target human genes such as miR4723–3p, miR5780d, and miR548d-3p targeting discs large MAGUK scaffoldprotein 2 (DLG2), NUMB endocytic adaptor protein (NUMB) and glycogen synthase kinase-3B (GSK3B) genes which were related to cancers such as breast cancer, lung cancer and leukemia [116]. *Ocimum basilicum* is a medicinal plant and its bioactive compounds have potential for therapeutic approaches. miRNA target prediction analysis revealed the target of *O. basilicum* miRNAs, miR156, miR531, miR160, miR529b, and miR1118 were 87 human target genes associated with the Ras-mitogen-activated protein kinase (Ras-MAPK) signaling pathway, Alzheimer disease, breast cancer, cardiomyopathy, HIV, lung cancer, and several neurological disorders [117].

Plants	Plant derived-miRNAs	Human target gene/ Disease	References
Oryza sativa	osa-miR156a osa-miR166a osa-miR168a	LDLRAP1	[105]
Populus euphratica	peu-miR2910	JAK–STAT pathway	[115]
Camptotheca acuminata	14 miRNAs	Cancer (breast, lung and leukemia)	[116]
Ocimum basilicum	miR156 miR531 miR160 miR529b miR1118	Ras-MAPK signaling pathway, Alzheimer disease, breast cancer, cardiomyopathy, HIV, lung cancer, several neurological disorders	[117]
Curcuma longa	miR14	Rheumatoid arthritis	[120]
cabbage, spinach and lettuce	miR156a	Cardiovascular disease	[118]
Oryza sativa	miR156-5p miR164-5p miR168-5p miR395-3p miR396-3p miR396-5p miR444-3p miR529-3p miR1846-3p miR2907-3p	Cancer, cardiovascular and neurodegenerative diseases	[119]

Table 2.
Dietary miRNAs and human gene regulation.

The abundantly expressed miRNA in dietary green vegetable, miR156a which was detected in human serum and targeted the junction adhesion molecule-A (JAM-A) [118]. The JAM-A was up-regulated in atherosclerotic lesions from cardiovascular disease patients and miR156a could suppressed inflammatory cytokine-induced monocytes adhesion by targeting JAM-A [118]. The very recently report using a computational approach to predict the potential target of rice miRNAs including miR156-5p, miR164-5p, miR168-5p, miR395-3p, miR396-3p, miR396-5p, miR444-3p, miR529-3p, miR1846-3p, miR2907-3p, which can bind to the human mRNA [119]. Most of these target genes were associated with cancer, cardiovascular and neurodegenerative diseases [119]. miR14 derived from *Curcuma longa* was detected and remarkably stable in human serum for 48 h. The potential targets of miR14 were associated with inflammation in rheumatoid arthritis such as Phosphotidylinositol-specific-phospholipase C (PLCXD3), Adenylate cyclase 9 (ADCY9), and 3′ (2′), 5′-bisphosphate nucleotidase (BPNT1) [120].

4. Conclusion

It has been widely known that functional foods and their bioactive compounds have the capacity for human health benefits. To date, miRNAs have been shown a significant effect on gene expression and modulate the cellular biological functions in physiological and pathological conditions. There is emerging evidence suggesting that dietary bioactive compounds can be effective in human diseases as a result of altering miRNAs expression levels, resulting in modulation of cellular signaling pathway. Additional research the possibility of bioactive compounds for developing as novel drugs with less side effects is required *in vitro* and *in vivo*. Recently, it has been revealed in several studies that dietary derived-miRNAs are bioavailable and alter human gene expression. The cross-kingdom gene regulations of dietary miRNAs from plants to human have raised our expectations for evaluating the active therapeutic potential and dietary supplements.

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