

Prospects**Diet and Cancer Prevention: Dietary Compounds, Dietary MicroRNAs and Dietary Exosomes[†]**

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Abstract

Cancer is one of main health public problems worldwide. Several factors are involved in beginning and development of cancer. Genetic and internal/external environmental factors can be as important agents that effect on emerging and development of several cancers. Diet and nutrition may be as one of important factors in prevention or treatment of various cancers. A large number studies indicated that suitable dietary patterns may help to cancer prevention or could inhibit development of tumor in cancer patients. Moreover, a large numbers studies indicated that a variety of dietary compounds such as curcumin, green tea, folat, selenium and soy isoflavones show a wide range anti-cancer properties. It has been showed that these compounds via targeting a sequence of cellular and molecular pathways could be used as suitable options for cancer chemoprevention and cancer therapy. Recently, dietary microRNAs and exosomes have been emerged as attractive players in cancer prevention and cancer therapy. These molecules could change behavior of cancer cells *via* targeting various cellular and molecular pathways involved in cancer pathogenesis. Hence, the utilization of dietary compounds which are associated with powerful molecules such as microRNAs and exosomes and put them in dietary patterns could contribute to prevention or treatment of various cancers. Here, we summarized various studies that assessed effect of dietary patterns on cancer prevention shortly. Moreover, we highlighted the utilization of dietary compounds, dietary microRNAs and dietary exosomes and their cellular and molecular pathways in cancer chemoprevention. This article is protected by copyright. All rights reserved

Key word: Diet, Dietary pattern, Dietary microRNA, Dietary exosomes, Cancer, Prevention

Introduction

Cancer is known as one of major public health problems which are associated with a public health concern worldwide (Ferlay et al., 2015). The assessing of different dimensions for this disease has led to identification of various factors involved in cancer pathogenesis. These findings could help to prevention and better treatment of various types of cancer (Mirzaei et al., 2016h; Mirzaei et al., 2016j). Various classes of factors participate in start and development of various cancers (Schottenfeld and Fraumeni Jr, 2006). Multiple lines evidences indicated that genetic and envirmetal factors involved in various stages of different malignancies (Schottenfeld and Fraumeni Jr, 2006). To date, researchers with more understanding of molecular/cellular pathways involved in different cancers could design many therapies and regimen for before and after cancer. But, with growth of human knowledge in the cellular and molecular pathways involved in different stages of cancers, obtain new data that could contribute be design novel therapies (Mirzaei et al., 2016d; Mirzaei et al., 2016h; Mirzaei et al., 2016j; Salarinia et al., 2016). Moreover, using of these data could lead to development of new therapies such as gene and cell therapy for treatment of cancer (Mirzaei et al., 2016d; Mirzaei et al., 2016f; Mohammadi et al., 2016b; Saadatpour et al., 2016b; Saadatpour et al., 2017). Among of various factors involved in start and development of cancer, life style has a main role. Human dietary patterns could effect on human health in various ways. The suitable nutrition regimen has important effects on human health (Couto et al., 2011). It observed that enough uptakes of various vitamins and fats could have positive effects on various diseases such as depression and cancer (Banikazemi et al., 2016; Banikazemi et al., 2015; Chen et al., 2015b; Mayne et al., 2016). Various studies indicated that suitable diet and dietary patterns may have key roles in prevention or even treatment of cancer (Chen et al., 2015b; Rodriguez et al., 2004). The intake of various fruits and diet with many antioxidant components may help be prevention of cancer. The

inflammation is known as one of main factors for development of many cancers (Albanes et al., 1995; Catsburg et al., 2015; Marmot et al., 2007; Mayne et al., 2016; Rodriguez et al., 2004). The utilization of suitable dietary including antioxidant components may effect on development of cancer and inhibition it (Albanes et al., 1995; Marmot et al., 2007; Mayne et al., 2016). It's found that a plant-based diet that limits red meat intake could be linked with reduced risk of breast cancer (Catsburg et al., 2015).

Dietary compounds are known as one of important therapeutic agents which could affect on a variety of cellular and molecular pathways (Chen and Kong, 2005; Langner and Rzeski, 2012; Pan and Ho, 2008). A large number studies indicated that the utilization of various dietary compounds including green tea, curcumin, selenium, carotenoids and vitamins could help to cancer prevention and treatment. Hence, it seems that the utilization of them in dietary pattern could be useful for cancer prevention and therapy (Chen and Kong, 2005; Langner and Rzeski, 2012; Pan and Ho, 2008). Recently, some studies indicated that dietary microRNAs and exosomes have critical roles in change behavior various cells such as cancer cells. MicroRNAs (miRNAs) are known as small non-coding RNAs which act as epigenetic regulators (Mirzaei et al., 2016a; Mirzaei et al., 2016g; Mohammadi et al., 2016a; Rashidi et al., 2016; Salarinia et al., 2016). These molecules have critical roles in a variety of cellular and molecular pathways involved in cancer pathogenesis (Gholamin et al., 2017; Mashreghi et al., 2017; Mirzaei et al., 2017a; Moridikia et al., 2017; Ross and Davis, 2014). Hence, these molecules could be used as diagnosis, and therapeutic biomarkers (Fathullahzadeh et al., 2016). It has been showed that dietary miRNAs could be as attractive tools for cancer prevention and therapy. Moreover, it has been showed that dietary exosomes and their cargos could be used as new candidate for cancer prevention and therapy (Ju et al., 2013; Mirzaei et al., 2017b; Record, 2013). Here, we summarized the role of dietary patterns on prevention of

cancer shortly. Moreover, we highlighted the utilization of dietary compounds, dietary miRNAs and dietary exosomes as powerful candidates for cancer prevention and therapy.

Dietary patterns and cancer

Multiple lines evidence indicated that many factors involve in different stages of cancer (Weiderpass, 2010). These factors (including genetic and environmental factors) play key roles in start and development of different cancers (Kolonel et al., 2004; Mayne et al., 2016; Weiderpass, 2010). Dietary patterns are probably known as one of important factors that may be associated with various cancers. Few studies have examined effect dietary patterns on cancer prevention (Chen et al., 2015b; Willett, 2000). Some evidences indicated that various dietary patterns cannot contribute to cancer prevention in different stages (Chen et al., 2015b). On the other hand, some reports revealed that a healthy diet with plenty of vegetables and fruit may decrease risk of cancer. These studies indicated that the utilizing of suitable dietary patterns and particular vitamins may contribute to cancer prevention in certain groups of patients (Weinstein et al., 2007). In a study, Rodriguez et al., found that intake of vitamin E supplements for male smokers could decrease risk of prostate cancer. Their results showed that supplementation with alpha-tocopherol (a form of vitamin E) can reduce risk of prostate cancer (Rodriguez et al., 2004). In four studies observed that vitamin E could decrease the risk of prostate cancer in past/recent and current smokers and those with low levels of this vitamin (Moyad, 2002; Weinstein et al., 2007). Moyad et al., found that selenium and vitamin E are probably 2 of the main dietary supplements which utilization of them could decrease prostate cancer risk (Moyad, 2002). Some reports revealed that there were no significant reduction between multivitamin, mineral supplementation and mortality or incidence of cancer, while some reports show a possible prevention effect in cervical cancer (Dolara et al., 2012). In 2012 a review of 9 studies assessed the effect of various vitamins and minerals on

lung cancer risk. Their results showed that there was no evidence for recommending supplements of vitamins A, C, E, selenium, either alone or in different combinations, for the prevention of lung cancer and lung cancer mortality in healthy people. Moreover, some evidence indicated that the use of beta-carotene supplements could be related with a small increase in lung cancer incidence and mortality in smokers or persons exposed to asbestos.(Cortes-Jofre et al., 2012) . Finally, there are no strong evidences that dietary supplements and dietary patterns can contribute to prevention, control and treat various cancers. But few small pilot studies have found that nutritional supplements and dietary patterns may contribute to prevention, treat and control of cancer for some subjects (Béliveau and Gingras, 2007; Chen et al., 2015b; Dolaro et al., 2012). Hence, choosing suitable dietary supplements can help to prevention of cancer and effective treatment during cancer. It seems that examining of various dietary patterns on cancer patients can be contribute to identifying of new dietary patterns that are effective on the prevention, treatment and control of various cancers.

Dietary compounds and cancer chemoprevention

Cancer chemoprevention is known as an approach which employed natural or synthetic agents to decrease or suppress cancer development and progression (Chen and Kong, 2005; Langner and Rzeski, 2012; Pan and Ho, 2008). It has been showed that dietary compounds could be used as a suitable therapeutic agent for cancer chemoprevention. The interesting of utilization of dietary compounds due to specific properties of them such as low toxicity compared with regular drugs. Multiple lines evidence indicated that a wide range of dietary chemo-preventive agents such as long-chain polyunsaturated fatty acids, green tea polyphenols (i.e. catechins), carotenoids, curcumin, vitamins (i.e. vitamin D and folate) glucosinolates/isothiocyanates, and minerals (i.e. calcium and selenium) could be introduced

into clinical application for cancer therapy (Chen and Kong, 2005; Langner and Rzeski, 2012; Pan and Ho, 2008) (Table 1) .

Curcumin is one of interesting phytochemicals which shows wide ranges anti-cancer properties (Mirzaei et al., 2016b; Mirzaei et al., 2016c; Mirzaei et al., 2017d). Several studies indicated that curcumin via targeting a sequence cellular and molecular pathways exert its therapeutic effects (Mirzaei et al., 2016b; Mirzaei et al., 2016c; Mirzaei et al., 2017d). A variety of cellular and molecular targets including microRNAs (miRNAs), NF- κ B, AP-1, COX-2, MMPs, cyclin D1, EGFR, Akt, β -catenin, adhesion molecules and TNF could be affected by curcumin (Mirzaei et al., 2016b; Mirzaei et al., 2016c; Mirzaei et al., 2017d; Simonian et al., 2017) (Figure 1).

Green tea is other natural components which is associated with wide ranges of therapeutic properties (Rashidi et al., 2017). It has been showed that this plant is a rich source of proteins (including enzymes), amino acids, carbohydrates, lipids, vitamins (B, C, E) and minerals (i.e. Ca, Mg, Cr, Fe, Zn, F, K) (McKay and Blumberg, 2002). Various studies indicated that is mostly therapeutic effects of Green tea is related with the abundance of polyphenols, particularly flavonoids. Catechins (flavan-3-ols) including including epicatechin (EC), epicatechin-3-gallate (ECG), gallocatechin (GC), epigallocatechin (EGC) and predominant (-)-epigallocatechin-3-gallate (EGCG) are one of important flavonoids present in green tea leaves (Langner and Rzeski, 2012). It has been that Green tea exerts its anti-cancer properties via inhibition of growth tumor via targeting cellular and molecular involved in cell proliferation, and angiogenesis. VEGFs are one of important targets which could be affected by this component (Rashidi et al., 2017).

Epigenetic mechanisms are important pathways which could be affected by dietary compounds in cancer chemoprevention (Hardy and Tollefsbol, 2011; Li et al., 2014). There

are different mechanisms including DNA methylation, histone modifications, and microRNAs (miRNAs) which act as epigenetic regulators (Mirzaei et al., 2016g; Salarinia et al., 2016). It has been indicated that dietary compounds could affect on cancer prevention via targeting of epigenetic mechanisms (Hardy and Tollefsbol, 2011; Li et al., 2014). A large number studies revealed that bioactive phytochemicals are able to change expression of a variety of oncogenes and tumor suppressor genes via targeting epigenetic mechanisms involved in cancer initiation and progression (Hardy and Tollefsbol, 2011; Li et al., 2014). Moreover, the utilization of bioactive phytochemicals alone or in combination with other natural or synthetic agents could be associated with significant results against a variety of cancers (Hardy and Tollefsbol, 2011; Li et al., 2014).

Finally, it seems that the utilization of dietary compounds and put them in dietary patterns could be associated with significant results against prevention of a variety of cancers. Hence, we offer that the utilization of them could be employed as powerful candidates in dietary patterns which may contribute to new insights into cancer prevention.

Dietary microRNA and cancer prevention

MicroRNA (miRNA) is small noncoding RNAs which acts as epigenetic negative/positive regulators in various physiological processes (Gholamin et al., 2016; Goradel et al., 2017; Hashemi Goradel et al., 2017; Mirzaei, 2017; Simonian et al., 2017). These molecules could act as a tumor suppressor or oncogene (Keshavarzi et al., 2017a; Rabieian et al., 2017). It has been showed that these molecules are able to regulate a wide range of cellular and molecular processes such as growth, angiogenesis, cell death, invasive and metastasis (Gholamin et al., 2017; Mirzaei et al., 2016i). Multiple line evidence indicated that deregulation of them could lead to disease condition (Hoseini et al., 2017; Keshavarzi et al., 2017b; Mirzaei et al., 2017c). A variety of miRNAs could affect on initiation and development.t of various types of

cancer. Hence, identification of them could contribute to better understanding of underlying cellular and molecular pathways and could lead to better treatment for patients with various diseases such as cancer. It has been showed that a variety of dietary compounds and bioactive foods could show inhibitory effects on cancer cells and also protective effects against cancer via modulating a variety of miRNAs involved in cancer pathogenesis (Nolte-t Hoen et al., 2015; Ross and Davis, 2011; Ross and Davis, 2014). A large number studies indicated that dietary compounds and bioactive foods could change expression of various miRNAs involved in various well known cancer processes such as angiogenesis, cell cycle regulation, apoptosis, differentiation, inflammation, metastasis and pathways involved in stress response (Cui et al., 2017; Neelakandan et al., 2012; Parasramka et al., 2012; Ross and Davis, 2011). Hence, understanding the affect of dietary compounds and bioactive foods on miRNA expression and miRNA function could provide new insight on prevention approaches to decrease the burden of cancer.

Many studies assessed effect of essential nutrients, and phytochemicals on regulation of miRNA expression in various types of cancer cells and other model systems. Few studies investigated the role of various dietary patterns (i.e. Western diet) or alterations in macronutrient content (i.e. caloric restriction) on expression of miRNAs and miRNA function (Zhu et al., 2011).

EGFR signals such as MYC and K-Ras are important signaling pathways which are associated with modulating of a variety miRNAs such as miR-143 and miR-145 in cancer tumorigenesis (Dougherty et al., 2009; Zhu et al., 2011). It has been showed that Western diet (known as a diet with high levels of animal fat and low levels of cholecalciferol and calcium) could induce colonic tumorigenesis via targeting EGFR signals (Newmark et al., 2001). It has been showed that Western diet via targeting EGFR could suppress miR-143 and miR-145

(known as tumor suppressor genes) which led to increasing colonic tumorigenesis and up-regulation of miRNA targets such as MYC and K-Ras (Zhu et al., 2011).

It has been showed that Dietary folate could be associated with regulation of miRNA expression in different model systems and this could be related to the activity of folate in cancer prevention and risk. In a study, Marsit et al., indicated that deficiency of folate in growth media of human lymphoblastoid cells could induce significant changes expression levels of 24 miRNA such as miR-222 (Marsit et al., 2006). They showed that when folate was added back to the media, expression profiles of miRNAs returned to that of control cells. These findings suggested that folate and some dietary components could modulate expression of various miRNAs and deregulation of these miRNAs might be suitable biomarkers of nutritional status in humans as well as participants in cancer prevention (Marsit et al., 2006).

Vitamin E is other dietary components which could regulate miRNA expression. In a study, Gaedicke et al., indicated that utilization of diet with vitamin E deficiency (α tocopherol, < 1 mg/kg diet; γ tocopherol, < 1 mg/kg diet) for 6 month than a vitamin E-sufficient diet (α tocopherol, 12 mg/kg diet; γ tocopherol, 24 mg/kg diet) could change miRNA expression in a rat model (Gaedicke et al., 2008). They showed that vitamin E deficiency could lead to decreasing of hepatic miR-122a and miR-125b expression. These miRNAs could be involved in lipid metabolism, inflammation, and HCC. These results suggested that providing of a dietary regimen with appropriate vitamin E status could exert its prevention regulatory properties via regulating miRNA expression which involved in cancer prevention (Gaedicke et al., 2008).

MiR-21 is one of important targets of curcumin which could be involved in a wide range of cancer associated pathways (Chen et al., 2015a). Deregulation of miR-21 is associated with initiation and progression of various cancers. It has been showed that curcumin exerts anti-

cancer properties via down regulation of miR-21 in various types of cancer. It has been showed that miR-21 acts as one of important players in a variety of cancer associated processes such as proliferation, apoptosis, metastasis and drug resistance (Melnik, 2015; Mudduluru et al., 2011; Roy et al., 2013; Yang et al., 2013). A large number studies confirmed that miR-21 exerts its pathological effects via affecting various downstream pathways including phosphatase and tensin homolog (PTEN)/phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), programmed cell death protein 4 (PDCD4) and NF- κ B pathways (Melnik, 2015). Moreover, It has been showed that curcumin could affect on various cancers via affecting on exosomes containing miR-21 which has critical roles in progression of cancer (Wang et al., 2017a). Hence, miR-21 is one of major targets of curcumin which curcumin and its analogs exert their therapeutic effect via modulating of it.

Multiple lines evidence indicated that dietary factors may have adverse effects on microRNA signaling and could induce various types tumor (Melnik, 2015). For example, some studies indicated that there are significant relation between melanoma incidence and BMI (Calo et al., 2016; Candido et al., 2014). Among of various cellular and molecular targets which involved in BMI, MiR-21 is one of important players in this area. It has been showed that miR-21 could be involved in adipocyte differentiation and up regulation of it could be associated with obesity in obese subjects (Chartoumpakis et al., 2012; Kang et al., 2013; Keller et al., 2011). In the other hand, inhibition of miR-21 could be associated with reduction of obesity in db/db mice (Seeger et al., 2014). In a study, Pandey et al., indicated that HFD-induced obesity could be related with increasing of melanoma progression via targeting Cav-1 and FASN expression in tumors from HFD mice (Pandey et al., 2012). Moreover, adipocytes could release exosomes containing various miRNAs which could affect on various pathways (Ferrante et al., 2015; Muller et al., 2011). These findings suggested

that dietary miRNAs and dietary exosomes containing miRNAs may have critical roles in progression of various types of cancer.

Dietary effects on exosomal microRNAs and their role in cancer prevention

Exosomes are known as nano vesicles with 50–100 nm in diameter. Exosomes consist of a lipid bilayer membrane and a variety of proteins (Wagner et al., 2015). Moreover, it has been showed that these nano-criers could carry a variety of molecules such as DNAs, small non-coding RNAs(i.e. microRNAs) and various proteins(Mirzaei et al., 2016e; Saadatpour et al., 2016a). It has been showed that exosomes play critical roles in cell-to-cell communication. These vehicles via targeting their cargos could change behaviors recipient cells. Multiple lines evidence indicated that exosomes have important roles in initiation and progression of a variety of diseases such as cancer (Mirzaei et al., 2016e; Saadatpour et al., 2016a). These vehicles via targeting their cargos to recipient cells could lead to activation/inhibition of a sequence of cellular and molecular pathways involved in cancer (Mirzaei et al., 2016e; Saadatpour et al., 2016a). Recently, few studies indicated that dietary exosomes could be used as effective tools for cancer therapy. In a study, Ju et al., indicated that grape exosome-like nanoparticles (GELNs) could induce intestinal stem cells and protect mice from DSS-induced colitis (Ju et al., 2013). They results indicated that GELNs are able to travel within the gut and migrate through the intestinal mucus. They could be taken up by mouse intestinal stem cells and could induce the proliferation of intestinal stem cells. These finding suggested that edible exosomes could be used as effective candidates for prevention and treatment of a variety of diseases (Ju et al., 2013).

One of important exosomes cargos are miRNAs. It has been showed that a variety of dietary components are able to modulate expression of miRNAs in various models (Wagner et al., 2015). These regulations could lead to decreasing of cancer risk. Hence, it seems that dietary exosomes via introducing various cargos such as miRNAs could exert their therapeutic. It seems that future studies could open new windows in this area.

It has been showed that only viable cells are able to synthesize and release exosomes that could carry miRNAs to recipient cells. Dietary factors with nutrigenomic effects may modify the miRNA composition and content of cell-derived exosomes (Cui et al., 2017; Neelakandan et al., 2012; Parasramka et al., 2012).

Recent efforts have been undertaken to use milk-derived exosomes for the encapsulation of curcumin which could enhance curcumin transport and drug effects. These results suggested that using milk-derived exosomes containing curcumin could induce therapeutic effects of curcumin in the better way than using curcumin alone (Vashisht et al., 2017).

Dietary exosomes and cancer promotion

Various types of cells such as Somatic cells, immune cells, tumor cells, and mammary gland epithelial cells especially during lactation could release abundant exosomes for mRNA-, protein- and miRNA-mediated cell-cell communication, which has favorable (breastfed infant) or adverse effects on human health (Melnik, 2015). Numerous studies indicated that bovine milk could provide various bioactive exosomal miRNAs (Reinhardt et al., 2012; Sun et al., 2013). MiR-29b is one of exosomal miRNAs which could be absorbed by humans in biologically meaningful amounts. The uptake of this could be associated with increasing its systemic circulation and leads to alteration of gene expression of the milk consumer (Baier et al., 2014; Melnik et al., 2013). It has been showed that almost 245 miRNAs could be

presented in cow's milk. These miRNAs could affect on 11,000 human genes in the human (Baier et al., 2014). Hence, Milk could be suggested as an epigenetic transfection system that could promote postnatal growth via transferring a variety of miRNAs involved in various cellular and molecular pathways (Melnik et al., 2013). Moreover, bovine miRNAs of cow's milk could be survived in various processing such as pasteurization, homogenization and refrigerated storage for over 2 weeks (Howard et al., 2015).

Exosomal miR-21 is one of major miRNAs present in cow's milk (Chen et al., 2010; Sun et al., 2013). It has been showed that increasing of milk consumption could be associated with progression of hepatocellular carcinoma (Duarte-Salles et al., 2014). It has been showed that interleukin 6 (IL-6) is able to induces STAT3-dependent miR-21 transcription in hepatocellular carcinoma (Loffler et al., 2007). In a study, Michaëlsson et al., indicated that there are a positive correlation between milk intake and high levels of IL-6 (Michaelsson et al., 2014). The increasing of serum IL-6 levels has been related with a worse prognosis of melanoma (Hoejberg et al., 2012; von Felbert et al., 2005). Milk exosomal miR-155 is other important molecules which could be involved in STAT3-mediated tumorigenesis (Cao et al., 2013). It has been showed that miR-155 could induce STAT3 expression via inhibition of cytokine signaling 1 (SOCS1) which is known as a target of miR-155 (Cao et al., 2013; Zhao et al., 2013). Up regulation of miR-21 and miR-155 could be related with progression of melanocytic lesions. Exosomal TGF β is other proteins which could be transmitted by commercial milk (Pieters et al., 2015). It has been showed that TGF β signaling induces up regulation of miR-21 via stimulating the processing of primary transcripts of miR-21 (pri-miR-21) into precursor miR-21 (pre-miR-21) by the DROSHA complex (Davis et al., 2008). Hence, milk exosomes could be associated with progression of cancer via targeting various miRNAs and proteins such as miR-21, miR-155 and TGF β .

Conclusion

Dietary patterns are known as one of main risk factors for various cancers. It has observed that various dietary patterns such as meat (red meat, processed meat, fish and processed fish) or sugary-diet pattern are associated with risk of various cancers. In addition, multiple lines evidences indicated that plant dietary patterns have many antioxidant and anti-inflammatory components such as vitamin E that may be suitable for prevention or treatment of various cancers. The effect of various dietary patterns for prevention or treatments of different cancer remains unclear yet. Hence, more studies for showing positive or negative roles of them in cancer prevention are still required to be done. Moreover, a large numbers studies indicated that dietary compounds, dietary microRNAs and dietary exosomes could have critical roles in cancer prevention and therapy. Dietary compounds including curcumin, green tea components, carotenoids, minerals and vitamins could affect on a variety of cellular and molecular targets which are involved in cancer initiation and progression. Hence, it seems that the applying of them in various dietary patterns could be useful for cancer prevention and therapy.

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Table 1. A variety of dietary compounds which are associated with anti-cancer properties

Dietary compound (s)	Cancer	Target gene (s)	Effect (s)	Citation
Green tea	Bladder	PI3K/Akt, Bcl-2 family	The enhancing of apoptosis	(Qin et al., 2007)
	Glioblastoma	MMP-2, MT1-MMP	Inhibition of tumor growth	(Annabi et al., 2002)
	Breast	VEGF	Inhibition of angiogenesis	(Sartippour et al., 2002)
Polyunsaturated fatty acids	Colon	COX-1 or COX-	Inhibition of tumor growth	(Boudreau et al., 2001)
	Breast	-	Inhibition of tumor growth	(Bartsch et al., 1999)
	Prostate	-	Inhibition of tumor growth	(Rose and Cohen, 1988)

Glucosinolates/isothiocyanates	Lung	-	Inhibition of growth tumor	(Kvåle et al., 1983)
	Stomach	-	Inhibition of growth tumor	(Chyou et al., 1990)
	Colon	-	Inhibition of growth tumor	(Steinmetz et al., 1994)
	Prostate	-	Inhibition of growth tumor	(Hsing et al., 1990)
Carotenoids	Colon	cyclin D1, Bcl-2 and Bcl-xL	Induce apoptosis and inhibition of tumor growth	(Palozza et al., 2007)
	Prostate	AKT, cyclin D1	inhibition of tumor growth	(Ivanov et al., 2007)
	Breast	RARalpha and Cx43	inhibition of tumor growth	(Chalabi et al., 2007)
Vitamin D	Colon	p21, MIB-1	inhibition of tumor growth	(Fedirko et al., 2009; Lamprecht and Lipkin,

				2001)
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Folate	Colon	COX2	inhibition of tumor growth	(Vaisman and Arber, 2002)
Selenium	Leukemia	cyclin B1	Inhibition of cell proliferation	(Fimognari et al., 2004)
Calcium	Colon	COX2	inhibition of tumor growth	(Vaisman and Arber, 2002)
Curcumin	Melanoma	COX-2	Inhibition of cell proliferation	(Niu et al., 2016; Pisano et al., 2016)
	Colon	-	Inducing apoptosis, ROS, and ER stress	(Zhang et al., 2017)
	Glioblastoma	-	Inducing apoptosis	(Wang et al., 2017)
	Gastric	p53, Bcl-2, Bax and c-Myc	Inhibition of cell proliferation,	(Liu et al., 2016)

			Inducing apoptosis	
Breast	miR-29b-1-5p, PPARG, RRM2, SRSF1and EPAS1		Inhibition of tumor growth	(Tajbakhsh et al., 2017; Zhou et al., 2017)
Head and neck			Inhibition of tumor growth	(Basak et al., 2015)
Lung	miR-30c		Increasing the sensitivity of Paclitaxel-resistant , Inhibition of tumor growth	(Lu et al., 2017)

Table 2. Dietary microRNA involved in cancer prevention

Dietary component	Cell line	MicroRNA	Expression in cancer	Citation
Folate	TK-6	miR-222	Up regulation	(Marsit et al., 2006)
RA	NB4	miR-15a	Up regulation	(Garzon et al., 2007)
		miR-15b	Up regulation	(Garzon et al., 2007)
		miR-16-1	Up regulation	(Garzon et al., 2007)
		let-7a-3	Up regulation	(Garzon et al., 2007)
		let-7c	Up regulation	(Garzon et al., 2007)
		let-7d	Up regulation	(Garzon et al., 2007)
		miR-223	Up regulation	(Garzon et al., 2007)
		miR-342	Up regulation	(Garzon et al., 2007)
		miR-107	Up regulation	(Garzon et al., 2007)
		miR-181b	Down	(Garzon et al., 2007)

			regulation	al., 2007)
RA	SK-N-BE, LAN5 and SHSY-5Y	miR-10a	Up regulation	(Foley et al., 2011)
		miR-10b	Up regulation	(Foley et al., 2011)
1,25(OH) ₂ D	HL60 and U937	miR181a	Down regulation	(Wang et al., 2009)
		miR181b	Down regulation	(Wang et al., 2009)
1,25(OH) ₂ D	MCF12F	miR-26b	Down regulation	(Peng et al., 2010)
		miR-200c	Down regulation	(Peng et al., 2010)
		miR-200b	Down regulation	(Peng et al., 2010)
		miR-182	Down regulation	(Peng et al., 2010)
		Let-7b	Up regulation	(Peng et al., 2010)
Sodium selenite	LNCaP	miR-34b	Up regulation	(Sarveswaran et al., 2010)
		miR-34c	Up regulation	(Sarveswaran et al., 2010)
EGCG	HepG2	miR-18a	Down regulation	(Tsang and Kwok, 2010)

		miR-34b	Down regulation	(Tsang and Kwok, 2010)
		miR-193b	Down regulation	(Tsang and Kwok, 2010)
		miR-222	Down regulation	(Tsang and Kwok, 2010)
		miR-342	Down regulation	(Tsang and Kwok, 2010)
		let-7a,	Up regulation	(Tsang and Kwok, 2010)
		miR-16	Up regulation	(Tsang and Kwok, 2010)
		miR-221	Up regulation	(Tsang and Kwok, 2010)
Curcumin	BxPC-3	miR-22	Up regulation	(Sun et al., 2008)
		miR-199a	Down regulation	(Sun et al., 2008)
Curcumin	MCF-7	miR-15a	Up regulation	(Yang et al., 2010)
		miR-16	Up regulation	(Yang et al., 2010)
DIM	MiaPaCa-2, Panc-1 and L3.6pl	miR-200b	Up regulation	(Li et al., 2009)
		miR-200c	Up regulation	(Li et al.,

				2009)
		let-7b	Up regulation	(Li et al., 2009)
		let-7e	Up regulation	(Li et al., 2009)
Isoflavones	MiaPaCa-2, Panc-1 and L3.6pl	miR-200b	Up regulation	(Li et al., 2009)
		miR-200c	Up regulation	(Li et al., 2009)
		let-7b	Up regulation	(Li et al., 2009)
		let-7e	Up regulation	(Li et al., 2009)
Genistein	PC-3	miR-221	Down regulation	(Chen et al., 2011)
		miR-222	Down regulation	(Chen et al., 2011)
Resveratrol	LNCaP	miR-150	Up regulation	(Dhar et al., 2011)
		miR-296-5p	Up regulation	(Dhar et al., 2011)
		miR-7	Down regulation	(Dhar et al., 2011)
		miR-17	Down regulation	(Dhar et al., 2011)

		miR-20a	Down regulation	(Dhar et al., 2011)
		miR-18b	Down regulation	(Dhar et al., 2011)
		miR-20b	Down regulation	(Dhar et al., 2011)
		miR-92b	Down regulation	(Dhar et al., 2011)
		miR-106a	Down regulation	(Dhar et al., 2011)
		miR106b	Down regulation	(Dhar et al., 2011)
SCFA butyrate	HCT-116	miR-17	Down regulation	(Hu et al., 2011)
		miR-20a	Down regulation	(Hu et al., 2011)
		miR-20b	Down regulation	(Hu et al., 2011)
		miR-93	Down regulation	(Hu et al., 2011)
		miR-106a	Down regulation	(Hu et al., 2011)
		miR-106b	Down regulation	(Hu et al., 2011)
Oleic acid	HepG2	miR-21	Up regulation	(Vinciguerra

				et al., 2009)
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Figure 1. Various cellular and molecular targets which regulated by curcumin and its analogs

