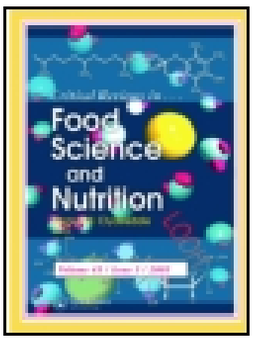

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MicroRNAs as molecular targets of quercetin and its derivatives underlying their biological effects: A preclinical strategy

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Abstract

Quercetin is a well-known flavonoid naturally occurring in most of the plant foods and is often found in the human diet. It can act as a potent antioxidant and anti-inflammatory agent, and plays significant roles in the prevention of various chronic diseases. Recent findings revealed that quercetin could affect metabolic traits by regulating certain transcription factors or key proteins involved in cellular signal pathways and influencing the expression of functional genes along with related regulatory pathway(s), and that microRNAs (miRNAs) circulate in body fluids and are involved in post-transcriptional gene silencing and regulation of gene expression in various biological processes including development, proliferation, metabolism and inflammation. This article reviews the studies into the molecular pathways underlying the beneficial bioactivities of quercetin and its derivatives, and the modulatory effects of miRNAs by quercetin and its derivatives on miRNAs-mediated cellular processes. MicroRNAs as molecular targets of quercetin and its derivatives and as predictive biomarkers for early diagnosis of the outcome of quercetin-rich diets are highlighted. Current limitations and future directions of research on the impact and associated mechanism(s) of the synergies between quercetin species and other co-existing nutrients/bioactives on the expression of miRNAs as well as the roles of miRNAs in overall nutritional control are critically discussed.

Keywords MicroRNA, quercetin, quercetin derivatives, multi-targeted, intercellular signalling, synergism.

Introduction

Healthy eating and active lifestyle are vital to human well-being. Many bioactive substances have been found to play significant roles in preventing, retarding and reversing certain diseases, including those particularly effective for various cancers such as flavonoids like quercetin (Linsalata et al. 2010;Angst et al. 2013). Quercetin and its derivatives (Fig. 1) are dietary components present in the human diet including foods such as onion, apple, tea, berries, wine, and other plant sources like seeds, nuts, flowers, barks and leaves. Quercetin and its derivatives can exhibit a wide spectrum of biochemical and pharmacological activities, which have been attributed largely to their direct antioxidant activities and anti-inflammatory properties (Patil et al. 2003). As functionally pleiotropic molecules, quercetin and its derivatives certainly exert impacts on multiple intracellular targets and cell signaling processes through separate and independent mechanisms e.g. modulating intracellular signaling cascades and activities of transcription factors and other regulators related to gene expression (Tripoli et al. 2007;Dajas 2012). The anticarcinogenic potential and therapeutic effects of quercetin and its derivatives are likely associated with their induction of cellular senescence and caspase-mediated apoptosis in hepatocellular carcinoma (HCC) cells, cell cycle arrest, p53 activation, suppression of telomerase and DNA polymerase-β, inhibition of nitric oxide and inducible nitric oxide synthases (iNOS) protein expression, inhibition of p300 signalling, binding ability to SEK1–JNK1/2 and MEK1–ERK1/2, binding impedance of cellular receptors and trans-activators such as activating transcription factor 4 (ATF4, former CREB2), c-Jun, CCAAT/enhancer-binding protein beta (C/EBPβ) and NF-κB to COX-2

promoter as well as the antioxidant-defense mechanisms (Fresco et al. 2006;Lee et al. 2006;Kampa et al. 2007;Zhao et al. 2014;Lewandowska et al. 2016).

MicroRNAs (miRNAs) are a class of endogenous, small, single-stranded, non-coding RNAs with 16~22 nucleotides and gene-regulatory properties. Over 2,000 miRNAs have been identified and approximately 30~90% of human genes are regulated by miRNAs (Lewis et al. 2005;Miranda et al. 2006;Pillai et al. 2007). The importance of these tiny molecules lies in their ability to regulate spatially and temporally the flow and expression of genetic information at the post-transcriptional level in the cytoplasm (i.e. at different cellular locations and binding sites). MiRNAs influence many cellular events including proliferation, differentiation, apoptosis and metabolism of cells, as well as intercellular signalling and energy metabolism (Fig. 2). Each miRNA can regulate from several to as many as hundreds of mRNAs and each mRNAs can also be targeted by different miRNAs (Lim et al. 2005;Bartel 2009), through which miRNAs monitor simultaneously a number of signalling pathways. They can bind to perfectly or imperfectly complementary sites in the 3′-untranslated regions (3′-UTRs) of target messenger RNA (mRNA) resulting in cleavage of mRNA or block of protein translation (Bartel 2004). Given the intimate involvement of miRNAs in cellular events as major controllers and their susceptibility to nutritional influences, miRNAs emerge as useful diagnostic or prognostic biomarkers and promising therapeutic targets for various diseases such as miR-29a, miR-221, miR-13-3p, miR-92a, miR-17-92, miR-135, miR-92a, miR-21, miR-143, miR-154, miR-106a and miR-144 (Bonfrate et al. 2013;Muhammad et al. 2014;Saplacan et al. 2015;Pan et al. 2017). Recent

studies have demonstrated that food components including nutrients and bioactive substances such as vitamins, lipids and phytochemicals (also called as “external stimuli” in some studies) can modulate miRNA expression and their pathways in a number of diseases such as cancer (Davis et al. 2008;Davidson et al. 2009;Izzotti et al. 2012;Parasramka et al. 2012;Shah et al. 2012). Not surprisingly, the relationship between miRNAs and quercetin as a bioactive phytochemical is of high interest. Mostly recently, several studies reported that quercetin offered protection against various diseases not only through influencing directly gene expression at an epigenetic or transcriptional level but also by modulating miRNAs as part of the post-transcriptional regulation of genes (Russo et al. 2017). However, there is a lack of systematic evaluation of literature to understand biochemical and molecular mechanisms of the protective action of quercetin against diseases, the molecular targets and signalling pathways implicated, and specific influence of quercetin on miRNA expression. The aim of present work was to evaluate recent evidence on the modulation of miRNAs expression by quercetin or its derivatives and the feasibility of combined uses of quercetin or derivatives and other dietary nutrients to enhance the health benefits of quercetin.

Quercetin and its derivatives

To understand the roles of quercetin in the prevention and treatment of various diseases, it is critical to examine not only quercetin itself but also its derivatives. Quercetin as a polyphenolic secondary metabolite is widespread in the plant kingdom including vegetables and fruits such as capers, lovage, onions, apples and berries. Dietary intake of quercetin differ between countries or regions accounting for about 75% of flavonoid intake (50 to 800 mg/day)

(Chun et al. 2007). Quercetin consists of two benzene rings (A and B) linked by a characteristic C6-C3-C6 carbon ring C with a benzo-(γ)-pyrone skeletal structure. In nature, quercetin occurs in both free state (as an aglycone) or in a bounded form (as derivatives), with the latter being dominant. Among quercetin derivatives, quercetin glycosides and ethers form the major group while quercetin sulfate and prenylated quercetin occur in much smaller quantities (Table 1) (Harborne et al. 2001;Biesaga et al. 2009;Chen et al. 2014). Quercetin glycosides are formed via glycosylation at the 3-hydroxyl or other hydroxyl group(s) between the hydroxyl group of quercetin molecule and a sugar moiety (i.e. monosaccharides, disaccharides or polysaccharides). Quercetin ethers (e.g. mono- or penta-ethers) are formed via conjugation of the quercetin hydroxyl group with alcohol (e.g. methanol). Prenylflavonols are formed via prenylation at the carbon atom of the quercetin skeleton. There might be more complex forms of quercetin, and the increased availability of advanced analytical technologies would facilitate their identification.

The potential biological effects of quercetin on human body are dependent on its existing form, metabolism after ingestion, and solubility and bioavailability at nutritionally relevant concentrations. Also, the biological functions of quercetin derivatives/metabolites are mostly site-specific in nature (Shimoi et al. 2001). The (inter)-conversions of quercetin to its derivatives or metabolites after ingestion should be considered during the evaluation on the biological effects of quercetin. Quercetin derivatives upon ingestion will undergo hydrolysis mostly in the gastrointestinal tract before absorption (Walle 2004). Quercetin is metabolized into degraded or altered structures by microbial actions and associated enzymatic reactions,

via molecular breakdown (e.g. degradation due to ring fission in the colon) or reconjugation (e.g. glucuronidation, methylation, sulfation or hydroxylation) (Kim et al. 1998;Scalbert et al. 2000;Simmering et al. 2002). Quercetin conjugates are the dominant forms in blood (including sulfate or glucuronidates with/without methylation on the catechol group of quercetin) e.g. quercetin-3-glucuronide, 3'-methyl-quercetin-3-glucuronide, quercetin-3'-sulfate, quercetin-3-glucoside or quercetin-4'-glucoside (Day et al. 2001;Sesink et al. 2001). In comparison, a relatively high proportion of free quercetin (aglycone) and 3'O-methylated quercetin isorhamnetin found in organs such as lung, liver and kidney (Németh et al. 2003).

Quercetin and its derivatives differ in chemical, physical and biological properties including solubility, polarity (hydrophilicity and lipophilicity), permeation across membrane, antioxidant activity, metabolism and bioavailability, owing to changes in molecular structure via substitution/conjugation with sugars, lipids, alcohols phenolic acids and sulfate residues (Rice-Evans et al. 1997;Cermak et al. 2003;Lin et al. 2003). The differences in chemical structure (including configuration, substitution, and number and location of hydroxyl groups) have considerable impacts on the reactions and mechanisms involved in their antioxidant actions such as capacity to scavenge radical species and their ability to chelate metals (Dangles et al. 2000;Boots et al. 2008). The conjugation position of quercetin may dramatically affect biological activity, partially due to the poor *in vitro* chemical reactivity of quercetin conjugated derivatives compared to quercetin (Lodi et al. 2008). A quercetin glycoside would exhibit much greater anti-inflammatory effect and immune-enhancement

than other forms of quercetin (Li et al. 2016). Quercetin-3-glucuronide would be metabolized upon inflammation, causing an increased amount of less active quercetin aglycone (Kawai et al. 2008).

Although quercetin is permeable, its bioavailability is low owing to poor solubility, greater extent of conjugation, potential toxicity to humans (xenobiotic-induced detoxification by the detoxification system consisting of phase II enzymes) (Kawanishi et al. 2005;Donovan et al. 2007;Lambert et al. 2007). Quercetin glycosides are normally too polar to penetrate the intestinal membranes causing difficulty in absorption. Therefore, chemical or enzymatic modification of the structures of quercetin species may improve their bioavailability and bioaccumulation (Terao 2017) e.g. appropriate glycosylation and prenylation using cell cultures as well as *in situ* cleavage of glycoside residues by microfloral enzymes at desired sites to yield more degradable quercetin aglycone (Murota et al. 2010;Chen et al. 2014). Prenylation can enhance the biological properties of quercetin by increasing hydrophobicity and bioavailability (Inui et al. 2012). Moreover, food matrix can influence the bioavailability of quercetin. Human subjects can absorb significant amounts of quercetin from food or supplements with a half-life for elimination as 11-28 hours (Manach et al. 2005) and an average terminal half-life as 3.5 hours (Konrad et al. 2015). But quercetin species in whole foods such as onion seemed to possess a higher bioavailability than in quercetin supplements (Shi et al. 2015;Petersen et al. 2016;Burak et al. 2017).

The natural co-occurrence of quercetin and its derivatives/metabolic products would complicate the evaluation and interpretation of the detected bioactivities of quercetin.

Different biological activities of quercetin species are probably associated with their different effects on cellular regulatory molecules including miRNAs.

MiRNAs-associated bioactivities of quercetin

Many distinct miRNA genes are now known to exist, and specific sets of miRNAs are associated with particular biological pathways. MiRNAs expression is tissue-specific and in response to both endogenous and exogenous stimuli (Bartel 2004;Pillai et al. 2007). Thus, strong tissue-specific miRNA signatures can be identified for cell lines or animal models to track the progress of a particular disease according to cell proliferation, cycle control, differentiation, migration, metabolism and apoptosis processes.

Quercetin possess anticancer activity, which is closely related to its anti-inflammatory activity in cancer where COX is overexpressed (Mutoh et al. 2000). Suppressing carcinogenesis is achieved through the inhibition of CYP450 family of enzymes (Lautraite et al. 2002) and radical scavenge by quercetin (Cerutti 1985), as well as through anti-inflammatory mechanisms involving inhibition of COX and LOX and reduction of COX transcription.

Anti-cancer effect

MiRNA genes would be subject to epigenetic changes in cancer following a similar fashion to protein coding genes. Numerous miRNA genes are positioned in cancer-associated genomic regions which would be dysregulated under cancerous conditions, and play crucial roles in cancer initiation, promotion and progression (Calin et al. 2004). As mentioned earlier, distinct miRNAs have been identified in specific cancer tissues and cultured cell lines (Ferdin

et al. 2010). In cancer, downregulation of anti-tumorigenic miRNAs is by oncogenic transcription factors (e.g. Myc) and by loss/mutation of tumour suppressor transcription factors (e.g. p53) (Chang et al. 2008;Muller et al. 2011).

Quercetin and its derivatives have exhibited promising anticancer effects (Murakami et al. 2008). Quercetin as a pleiotropic agent can modulate at least 48 miRNAs including those that reduce tumor metastasis and invasion (miR-146a/b, 503 and 194), inhibit cell proliferation (miR-125a, 142-3p, 155, let-7 family, 302c, 195, 26a, 503 and 215), induce apoptosis (miR-125a, 27a, 605, 26b, let-7g, 34a, 491 and 16), and upregulate tumor suppressor miRNAs (let-7 family, miR-125a, 183, 146a, 98, 19b, 106a and 381) (Noratto et al. 2011;Lam et al. 2012;Del Follo-Martinez et al. 2013;MacKenzie et al. 2013;Appari et al. 2014;Lou et al. 2015). Quercetin may prevent carcinogenesis by up-regulation of tumor suppress or miRNAs (like let-7 family and miR-125a) and down-regulation of oncogenic miRNAs (like miR-27a) (Khan et al. 2016). For instance, Lam et al. (2012) reported the influence of quercetin-rich food intake on miRNA in 264 lung cancer cases, and the differential expression of key biologically functional miRNAs found between consumers with high or low intake of quercetin, among which were let-7, miR-146, miR-26 and miR-17 families from family-based analyses as well as 33 unique miRNAs from individual-based analyses.

The link between miRNAs and cancer progression induced by quercetin was comprehensively described in mechanistic studies presenting that important genes involved in key signaling pathways of carcinogenesis such as Notch, epidermal growth factor receptor

(EGFR), k-RAS, tumor protein 53 (p53) and NF-κB that were affected by miRNA expression. For example, Notch pathway was down-regulated by let-7c and miR-200b-3 (Nwaeburu et al. 2016;Nwaeburu et al. 2017). In addition, miR-146a up-regulation led to EGFR inactivation (Tao et al. 2015), similarly, the inhibition of NF-κB pathway was associated with miR-146a (Bhaumik et al. 2008;Sha et al. 2013). Consequently, these pathways in turn led to related modification in the main stages of cancer development.

A well-known tumor suppressors, let-7 family, was strongly up-regulated among lung cancer cases consuming quercetin-rich foods and a key member of which, let-7a, a suppressor of *k*-RAS and c-Myc oncogenes, showed the largest fold change (Lam et al. 2012). In another cell model, quercetin treatment of pancreatic ductal adenocarcinoma (PDA) cells up-regulated let-7c, which could induce indirect inhibition of Notch pathway signaling through activation of Numbl (Table 2) (Nwaeburu et al. 2016). Likewise, in pancreatic cancer stem cells (CSCs), this group presented quercetin's ability to increase miR-200b-3 that in turn lessened Notch signaling, which induced inhibition of self-renewal and decrease of proliferation of CSCs (Nwaeburu et al. 2017). In addition, let-7 family miRNAs and argonaute1 (AGO1) may coordinate the vascular endothelial growth factor (VEGF) desuppression and synthesis to control angiogenesis which has been found important in tumor development (Zhao et al. 2015). MiR-34 is another important tumor suppressor that attacks tumor-initiation and leads to apoptosis, cell-cycle arrest, and anti-angiogenesis (Chang et al. 2007;Ji et al. 2009;Javeri et al. 2013). Lou et al. (2015) disclosed that as a tie molecule, miR-34a was a component of a positive feedback loop between the p53 and SIRT1, which

could enhance the stability of p53 and promote the p53 related apoptosis in HepG2 cells exposed to quercetin . Tao et al. (2015) conducted two human breast cancer cell lines, MCF-7 and MDA-MB-231, and were able to demonstrate that quercetin favored apoptosis through caspase-3 activation and mitochondrial-dependent pathways, and inhibited invasion through down-regulating the expression of EGFR, which was mediated by up-regulation of miR-146a. Furthermore, it was reported that miR-146a induced apoptosis via inhibiting the expression of IRAK1 and TRAF-6 which were the upstream molecular of nuclear factor-kappa B (NF-κB), followed by suppression of NF-κB activity (Bhaumik et al. 2008;Crone et al. 2012;Xu et al. 2012;Sha et al. 2013). Especially, in colon cancer cells, yaupon holly leaves containing quercetin were identified in their potential role in the up-regulation of miR-146a as a post-transcriptional regulator of NF-κB and toll-like receptors 4 (TLR4) (Noratto et al. 2011). MiR-21 featured a prominent example of an oncomir which was a regulator of IGF-R1/PI3K/Akt pathway in various cancers and modulated the expression of phosphatase and tesin homolog (PTEN) and programmed cell death-4(PDCD4) genes involved in cell proliferation and apoptosis (Krichevsky et al. 2009). In BEAS-2B cells, quercetin exerted its protective effects against hexavalent chromium [Cr(VI)]-induced carcinogenesis and cytotoxicity by targeting miR-21-PDCD4 signaling in a dose-dependent manner (Pratheeshkumar et al. 2017).

Some other miRNAs and corresponding intracellular signallings, which were implicated in anticancer property of quercetin, including miR-16/claudin-2 in lung adenocarcinoma A549 cells (Sonoki et al. 2015), miR-142-3p/HSP70 in pancreatic ductal adenocarcinoma (PDAC)

(MacKenzie et al. 2013), etc., have also be reported by recent literatures. Collectively, these data proved that quercetin exhibited anti-carcinogenesis activity through anti-proliferative as well as proapoptotic mechanisms. The above-mentioned studies about miRNAs targeting NF-κB provided evidence that quercetin also modulated anti-inflammatory proteins in cancer cells to confer its anticancer effects.

Anti-inflammatory effect

Inflammation is the process of innate immunity in response to physical, physiological and/or oxidative stress which is associated with several signal transduction pathways (Ben-Neriah et al. 2011). Among these pathways, NF-κB, known as a crucial and complicated player in modulation of immune response, is a master switch of inflammatory genes and may regulate biomarkers of inflammation (such as IL1β, IL6, iNOS and TNFα) (Disis 2010).

Regarding the impact of quercetin as an inhibitor on inflammatory gene and miRNA, proinflammatory miR-155 was found to be down-regulated by quercetin, and in turn decreased mRNA and protein levels of tumor necrosis factor alpha (TNFα) in lipopolysaccharide (LPS)-induced murine RAW264.7 macrophages (Boesch-Saadatmandi et al. 2011). In a mouse model of high fat diet-induced chronic subacute inflammation, quercetin significantly increased the hepatic expression of miR-125b and miR-122 thereby contributing to the down-regulation of NF-κB activity and inflammatory gene expression (Boesch-Saadatmandi et al. 2012).

Other biological effects

Given various biological functions of quercetin as well as multiple roles of miRNAs in metabolic homeostasis, physiology and disease (including cell activities and metabolism of energy-related nutrients), it is not surprising that miRNAs expression controlled by quercetin could contribute to multi-step metabolic processes. So far, much research has been focused on miRNA-targeted modulation of quercetin against many cancers, but very limited data are available against chronic metabolic diseases such as cardiovascular disease. Garelnabi et al. (2014) discovered that the combination of quercetin and exercise had a dramatic impact on the cellular events involving a set of miRNAs signalling including miR-21, 125b and 451 in mice fed with an atherogenic diet. In another study, miRNA-array analysis showed that the 228 miRNAs of the rats supplemented with quercetin and the control rats differed in relative expression. From further study, two miRNAs (miR-19a and miR-19b) were found to have potential target genes involved in lipid metabolism and carbohydrate metabolism, indicating research direction for examining the mechanisms of repressive action of quercetin on obesity at miRNA level (Wein et al. 2014). Using microarrays, Wein et al. (2015) found that a nine-fold reduction in hepatic miR-125b-3p was paralleled by significantly increased GGH mRNA which were repeatedly associated with the resistance to methotrexate in the liver of rats fed with quercetin as compared to the control rats. Milenkovic et al. (2012) used microarrays to analyze the global miRNA expression and mRNA profiles in the livers of wild-type (C57B6/J) mice or apolipoprotein E-deficient mice administrated a control diet or diets supplemented with one of nine polyphenols. They also reported that quercetin, when

supplemented at 0.02%w/w for 2 weeks, could modulate expression of a number of miRNAs (n = 47) in the liver of apolipoprotein E-deficient mice.

MiRNA modulated by quercetin derivatives or metabolites

Besides quercetin, various quercetin derivatives and metabolites exist. Indeed, the difference in the position of conjugation of quercetin may lead to dramatic changes in biological activity, (as shown in Table 1). However, only very limited information is available on the exact nature of quercetin derivatives or metabolites and their influence on miRNAs expression. Quercetin and its methylated derivative isorhamnetin (rather than its major metabolites quercetin-3-glucuronide) significantly decreased mRNA and protein levels of tumor necrosis factor alpha (TNFα), and down-regulated proinflammatory miR-155 in lipopolysacharide–stimulated murine macrophages (Table 2) (Boesch-Saadatmandi et al. 2011). Rutin (quercetin-3-O-rutinoside) and quercetin 3-O-rutinoside-7-O-*α*-L-rhamnosidase exhibited anti-adipogenic effects and hypolipidemic activities through the repression of lipid metabolism-related miRNA expression (e.g. miR-33 and miR-122) (Su et al. 2017). Hyperoside, the 3-O-galactosideof quercetin, could ameliorate glomerulosclerosis in diabetic nephropathy via the down-regulation of miR-21 to increase expression of its target, matrix metalloproteinases (MMP)-9 (Zhang et al. 2016). A quercetin ether, rhamnetin (7-O-Methylquercetin) was found to enhance the radiotherapeutic efficacy and inhibited epithelial-mesenchymal transition (EMT) by miR-34a mediated suppression of Notch-1 signalling in non-small cell lung cancer cell lines (NSCLC) (Kang et al. 2013).

Potential synergies of quercetin and other nutrients or bioactive substances

Growing interests exist in examining the potential of miRNAs as promising diagnostic biomarkers because of their unique features such as high tissue specificity, good sensitivity and stability such as miR-143, associated with adipogenesis (Lynn 2009), miR-150 with diet-induced obesity (Watanabe et al. 2011), miR-155 and miR-196 with colorectal cancer and obesity (Volinia et al. 2006).

Increasing consumer awareness of the relationship between diet and health stimulates investigations on diagnostic tools capable of predicting and assessing the influence of dietary components on the incidence of certain diseases (including those at cellular and molecular levels). Moreover, it is recognized that the biological activities of the isolated bioactives (e.g. those in form of dietary supplements) do not equate the health benefits of the whole foods rich in these bioactives (e.g. fruits, vegetables and whole grains) (Liu 2004), and the synergistic effects of the bioactives and co-existing components are likely the main cause reason (Joven et al. 2014). Accordingly, consumption of a wide variety of foods can prevent chronic diseases, and intake of foods rich in certain bioactive(s) would help treat a particular disease (Liu 2004). A high-fat diet (20% fat versus 5% fat in standard diet) could down-regulate tumor suppressor miRNA-143 and miRNA-145 through epidermal growth factor receptor (EGFR) signalling (Zhu et al. 2011), and a high red meat (HRM) diet would lead to up-regulation of oncogenic miR-17-92 cluster and miR-21 (Humphreys et al. 2014).

Natural food components with anti-inflammatory properties (Mutoh et al. 2000;Jurenka 2009;Tili et al. 2011;van Harten-Gerritsen et al. 2015) and/or ability to influence cell events

(Delmas et al. 2004;Johnson et al. 2009;Shan et al. 2009;Watanapokasin et al. 2011;Ahmad et al. 2012;Larriba et al. 2013;Hu et al. 2015;Zhang et al. 2015) can modulate the expression of miRNAs. For examples, 46 miRNAs including let-7, miR-27a, miR34a, miR-142-3p, miRNA-146a, miR-125a, miR-605, miR-26b, miR-491, miR-155, miR-33, miR-122 and miR-16 for quercetin and derivatives (Boesch-Saadatmandi et al. 2011;Noratto et al. 2011;Lam et al. 2012;Del Follo-Martinez et al. 2013;MacKenzie et al. 2013;Appari et al. 2014;Lou et al. 2015;Su et al. 2017), miR-21, miR-622, miR-663, miR-17-92, miR-106a,b, miR-96 and miR-34a for resveratrol (Tili et al. 2010;Dhar et al. 2011;Han et al. 2012;Kumazaki et al. 2013;Liu et al. 2013;Saud et al. 2014), 61 miRNAs including miR-16, miR-92, miR-93, miR-106b, miR-7-1, miR-34a, miR- 99a, miR-210, miR-453, miR-520-e, miR-629 and miR-608 with epigallocatechin-3-gallate (EGCG) (Tsang et al. 2010;Wang et al. 2011;Chakrabarti et al. 2012), miR-21, miR-15a, miR-16, miR-34a, miR-34c, miR-27a, miR-181b and let-7a for curcumin (Han et al. 1999;Yang et al. 2010;Subramaniam et al. 2012;Kronski et al. 2014), miR-21, miR-27a, miR-34a, miR-574-3p, miR-151, miR-1260b, miR-146a, miR-23b-3p, let-7, miR-200, miR-221, miR-222 and miR-223 with genistein (Li et al. 2009;Sun et al. 2009;Chen et al. 2011;Chiyomaru et al. 2012;Zaman et al. 2012;Chiyomaru et al. 2013;Chiyomaru et al. 2013;Ma et al. 2013), miRNA-143 and miR-133b with α-mangostin (Nakagawa et al. 2007;Kumazaki et al. 2015), let-7e, miR-370, miR-373, miR-526b and let-7(a-d) with ellagitannins (Heber 2008;Wen et al. 2009), let-7 family, miR-1903, miR-467c, miR-3068 and miR-297a with (ω-3)-polyunsaturated fatty acids (Davidson et al. 2009;Tsoukas et al. 2015), miR-22 and miR-627 with vitamin D

(Alvarez-Díaz et al. 2012;Padi et al. 2013), miR-122a and miR-125b with tocopherol (vitamin E) (Gaedicke et al. 2008), miR-34a, miR-15a, miR-18a, miR-2861, miR-302b, miR-382, miR-487a, miR-760, miR-10a, miR-135a, miR-299-3p, miR-3126-5p, miR-3153, miR-411, miR-4321, miR-486-5p, miR-505, miR-598, miR-601 and miR-939 with tocotrienols (Kumar et al. 2011;Ji et al. 2012), miR-17-92 and miR-106b with dietary fiber (Hu et al. 2011;Humphreys et al. 2013).

Given the existence of various dietary components capable of modifying expression of miRNAs, one may wonder if any synergistic effects among these dietary components in the prevention and treatment of specific diseases. Interestingly, overlapping targeted miRNAs or mRNAs were found among different dietary bioactive components, therefore, bioactive compounds might share the same molecular miRNAs targets (Fig. 3). In fact, synergies between certain bioactive substances in modulating miRNAs have been found e.g. the resveratrol-quercetin combination with miRNA-27a (Del Follo-Martinez et al. 2013), ω-3-polyunsaturated fatty acids in fish oil-pectin (soluble fiber) with miR-19b, miR-26b and miR-203 (Priego et al. 2008;Shah et al. 2011), EGCG-enhanced effects of cisplatin (a well-known chemotherapeutic drug) through decreasing the level of miR-98-5p in A549 lung cancer cells (Zhou et al. 2014). Synergistic effects were obtained from the combination of garcinol and gemcitabine in pancreas cancer cells including up-regulation of miR-638 (0.65-fold), miR-720 (0.41-fold), miR-453 (4.78-fold) and miR-663 (0.92-fold), and down-regulation of miR-196a (0.82-fold), miR-495 (1.26-fold), miR-1914 (1.85-fold), miR-605 (2.42-fold) and miR-483-3p (1.06-fold) (Parasramka et al. 2013). Curcumin in

combination with 3-acetyl-11-keto-b-boswellic acid (AKBA) exhibited synergies in up-regulation of the tumor suppressor miR-34a in colon cancer cells (Toden et al. 2015). Curcumin in combination with emodin led to synergistic effects in up-regulation of miR-34a and suppression of miR-34 targets Bcl-2 and Bmi-1 associated with inhibition of breast cancer cell proliferation and invasion (Guo et al. 2013).

In terms of quercetin, its low bioavailability hinders its application and a high pharmacological dose of quercetin via oral administration may cause toxicity and other side effects (Terao 2017). Dietary quercetin would be converted to various forms of derivatives after extensive intestinal and hepatic metabolism, thus causing changes in its initial bioactivity in human body (Day et al. 2001;O'Leary et al. 2001;Sesink et al. 2001). Desired protection on quercetin and optimal bioactivities of quercetin are possible based on the synergy between quercetin and other phytochemicals in a non-toxic manner. On the other hand, as predictive biomarkers involved in many biological processes, miRNAs could act synergistically to regulate individual genes and demonstrate functional connections via cooperative participation in the same signalling process (Xu et al. 2011;Gennarino et al. 2012;Zhu et al. 2013). Therefore, exploitation of miRNAs as therapeutic targets for examining the synergism between phytochemicals and underlying mechanisms may be a promising approach. However, only a number of studies have been reported on modulation of miRNA(s) jointly by quercetin and other botanical compounds. In human HT-29 colon cancer cells, quercetin in combination with resveratrol suppressed oncogenic miR-27a causing enhanced induction of apoptosis through down-regulation of specificity protein (Sp)

transcription factors (Del Follo-Martinez et al. 2013). The combination of sulforaphane, quercetin and natural green tea catechins enhanced the expression of let-7a associated with inhibition of K-Ras signalling in suppression of pancreatic cancer cells and tumor growth (Appari et al. 2014). In androgen-dependent prostate cancer cell lines, treatments with low doses of both arctigenin and quercetin could synergistically enhance anti-proliferative effect by 30% (combination index: 0.2~0.8) compared to using either compound, which was partially due to significant reduction of miR-21, miR-19b and miR-148a, and consequent inhibition of arcinogenesis through PI3K/Akt pathway (Wang et al. 2015). Strong synergism between quercetin and hyperoside confers enhanced anticancer effects on 786-O renal cancer cells and PC3 prostate cancer cells, and the underlying mechanisms are associated with the down-regulation of miR-27a-ZBTB10-Sp1 and miR-21-PDCD4 axis, respectively (Li et al. 2014;Yang et al. 2015). It is worth noting that consumption of foods rich in bioactives including flavonoids like quercetin could lead to modification of miRNA expression e.g. up-regulation of miR-135b, miR-196a and miR-21 induced by a grape seed extract rich in flavonoids (Derry et al. 2013), up-regulation of miR-24 and miR-183 (Shirode et al. 2014) with reduced miR-27a level in breast cancer cells (BT-474, MDA-MB-231) by a pomegranate extract rich in ellagitannins punicalagin A, punicalagin B and anthocyanins (delphinidin-3-glucoside and cyanidin-3-glucoside) (Banerjee et al. 2012).

Conclusions

The current review presents the initial evidence that cellular targets of polyphenols could be regulated at the mRNA and miRNA levels. MiRNAs can act as an important intracellular target of quercetin and its derivatives, and overlapping targeted miRNAs or key regulatory genes exist among different dietary bioactives and are involved in different biological processes including physiological responses. Thus, synergies between quercetin or its derivatives and other bioactives in modulating miRNAs are possible.

A large number of studies have shown the co-occurrence of quercetin derivatives in nature and significant structural changes in quercetin and its derivatives during metabolism (yielding various metabolites in different locations inside the human body). Hence, investigations on miRNA modulation by quercetin metabolites and derivatives would be more important than on traditionally *in vitro* bioactivities of quercetin itself. Even for *in vivo* studies, the precise mode of action for cellular effects and actual form of quercetin (aglycone, derivatives or metabolites) for the interactions with miRNAs or protein-coding gene should be clarified. Data available suggested that the modulation of transcriptional factors, alteration in miRNA processing or epigenetic changes could be involved in the regulation of miRNA expression. Accordingly, future work should be directed towards the miRNA-based mechanisms of cardiovascular and metabolic diseases by quercetin species alone or via interactions with co-existing bioactives or other food components. Appropriate integration of the roles of miRNAs in post-transcriptional gene expression and silencing, and the impact of the synergies among quercetin derivatives/metabolites, or between quercetin species and other

co-existing nutrients/bioactives on the expression of miRNAs, would lead to successful development of novel and effective therapeutics to prevent and treat various illness and diseases.

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Figure caption

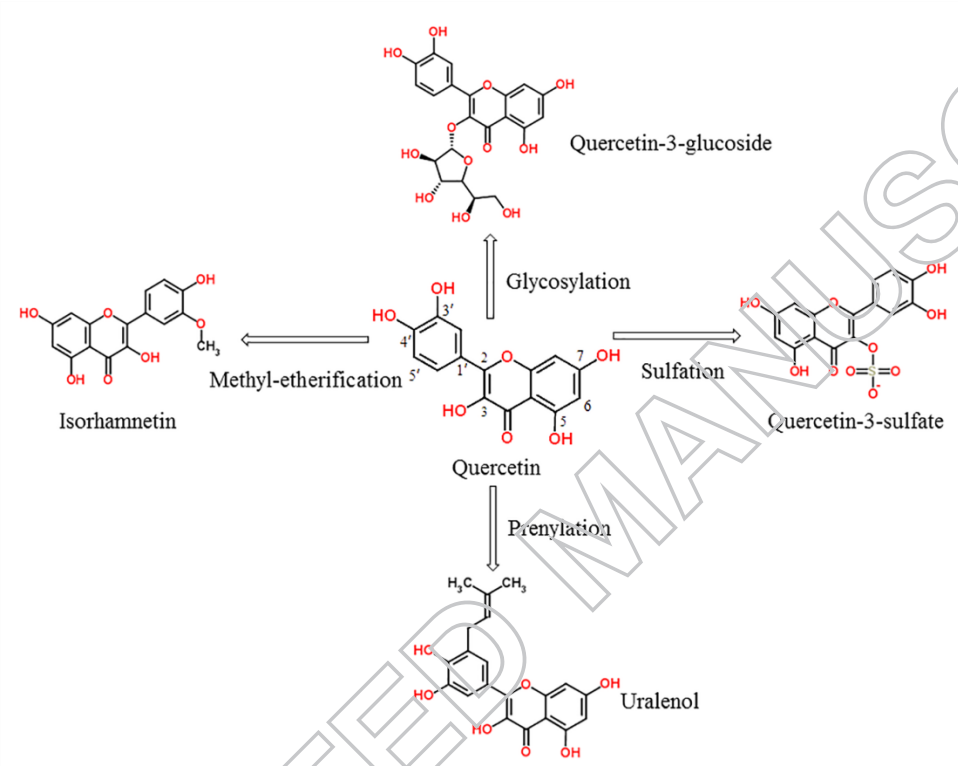

Fig. 1 Chemical structures of quercetin and its main derivatives (Glycosylation can occur at 3, 7 and/or 6 positions; Methyl-etherification can occur at 5, 7, 3' or 4' positions; Prenylation can occur at 5' position only or both 6 and 5' positions; Sulfation likely occurs at 3 position).

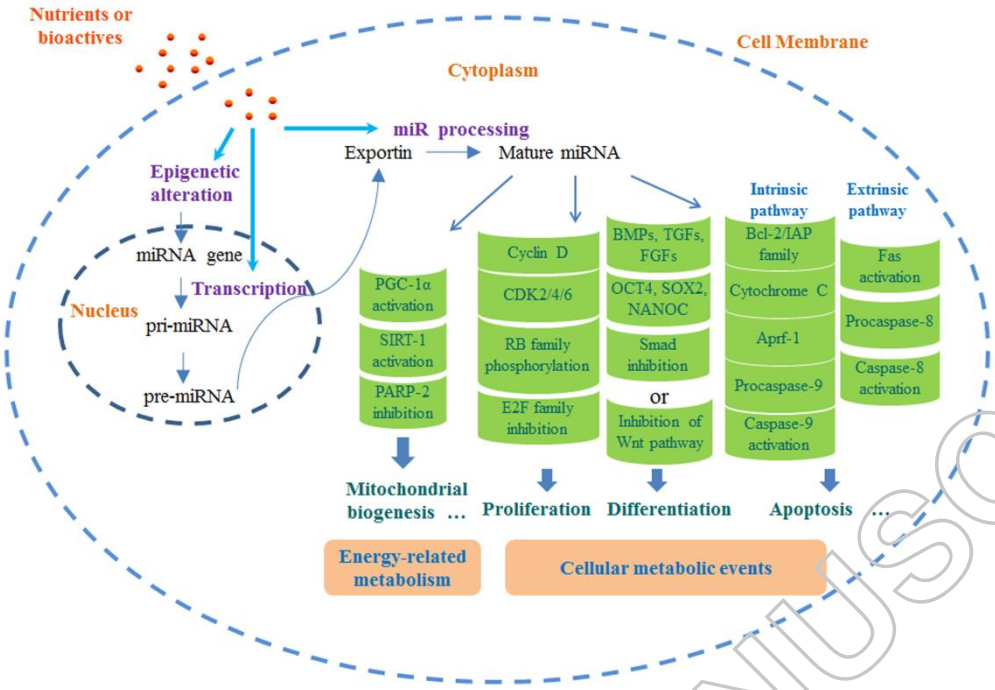

Fig. 2 Roles of MicroRNAs (miRNAs) in cellular metabolic events and energy-related metabolism by nutrients and bioactives.

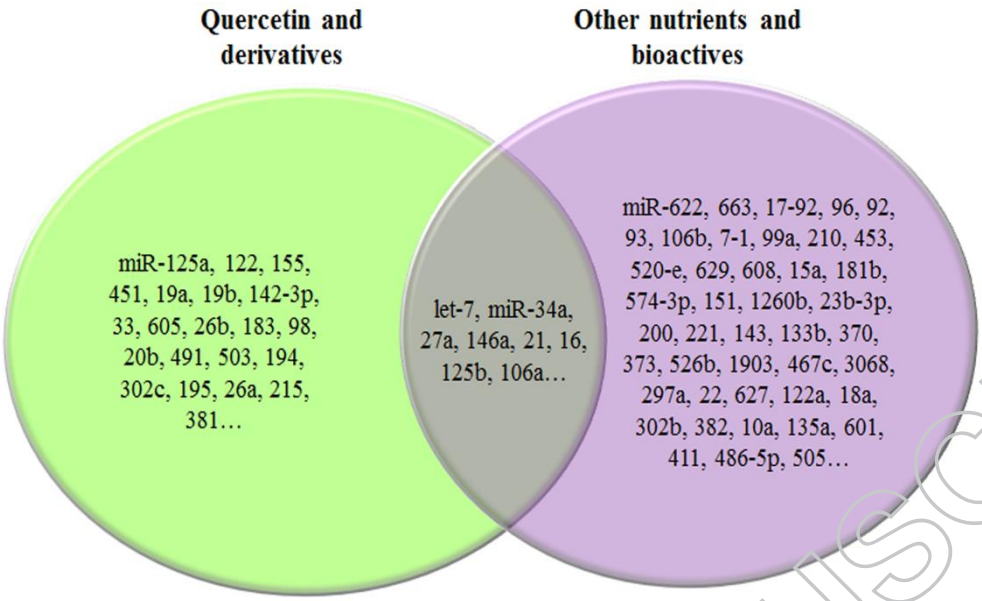

Fig. 3 A demonstration of some microRNAs (miRNAs) including overlapping miRNAs modulated by quercetin or its derivatives and other bioactives/nutrients.

Table 1 Some important properties of quercetin and its derivatives

Characteristics	Quercetin (aglycone)	Quercetin glycosides	Quercetin ethers	Prenylated quercetin	Quercetin sulfate
Chemical structure examples		With moieties e.g. monosaccharides (glucose, galactose, rhamnose, xylose, etc), disaccharides, polysaccharides or glucuronide	Quercetin methyl ethers, Rhamnetin, isorhamnetin, rhamnazin	Solophenol D, uralenol, 8-prenylquercetin	Quercetin 3,7,3′,4′-tetrasulfate
Solubility	↓ water solubility	↑water solubility	↓ water solubility	water-insoluble	↑ water solubility
Nature of occurrence	Naturally occurring or during metabolism	Naturally occurring, via synthesis or during metabolism	Naturally occurring, via synthesis or during metabolism	Naturally occurring, via synthesis or during metabolism	Naturally occurring, via synthesis or during metabolism
Anticancer effect	YES	YES	YES	YES	None in absence of sulfatase activity
Antioxidant activity	YES	YES	YES	YES	YES
Anti-inflammatory effect	YES	YES	YES	YES	YES
Other related functions	Immuno-stimulatory, immune-enhancement anti-allergic, psychostimulant, hepatoprotective	Immuno-stimulatory, immune-enhancement anti-allergic, psychostimulant, hepatoprotective	Preventing endothelial dysfunction, hypertension and cardiovasc	Antibacterial	Anticoagulant

	, antimicrobial	, antimicrobial		ular diseases	

Table 2 Modulation of miRNA expression, molecular targets and biological effects of quercetin and derivatives

Quercetin Type	**miRNA Target**	**mRNAor protein Target**	**Experimental Model**	**Biological Effect**	**References**
Quercetin	↓let-7c	↑numbl, ↓Notch	PDA cells	Inhibition of tumor growth	(Nwaeburu et al. 2016)
Quercetin	↑miR-200b-3	↓notch	Pancreatic CSCs	Inhibition of proliferation	(Nwaeburu et al. 2017)
Quercetin	↑miR-34a	↑p53, ↓SIRT1	HepG2 and Huh7 cells	Induction of apoptosis	(Lou et al. 2015)
Quercetin	↑miR-146a	↑caspase-3, ↓EGFR	MCF-7 and MDA-MB-231 cells	Induction of apoptosis and inhibition of invasion	(Tao et al. 2015)
Quercetin	↑miR-146a	↓NF-κB, TLR4	CCD-18Co cells	Anti-inflammatory	(Noratto et al. 2011)
Quercetin	↓miR-21	↑PDCD4	BEAS-2B cells	Inhibition of malignant cell transformation	(Pratheeshkumar et al. 2017)
Quercetin	↓miR-155	↓NF-κB, ↑Nrf2	LPS-induced murine RAW264.7 cell	Anti-inflammatory	(Boesch-Saadatmandi et al. 2011)

Quercetin	↑miR-125b, 122	↓NF-κB	Mouse model of high fat diet	Anti-inflammatory	(Boesch-Saadatmandi et al. 2012)
Quercetin	↑miR-21, ↓miR-451	--	C57BL6 $LDL^{-/-}$ mice fed atherogenic diet	Antioxidant	(Garelnabi et al. 2014)
Quercetin	↓miR-19a, 19b	--	Male Wistar ratsfed high-fat or low-fat diet	Anti-obesity	(Wein et al. 2014)
Isorhamnetin	↓miR-155	--	LPS-induced murine RAW264.7 cell	Anti-inflammatory	(Boesch-Saadatmandi et al. 2011)
Rutin	↓miR-33, 122	↑ABCA1, CPT1a, ↓FAS	Mouse model of high fat diet	Anti-adipogenesis	(Su et al. 2017)
Hyperoside	↓miR-21	↑MMP-9	Male C57BL/KsJ type 2 diabetic db/db mouse model	Inhibition of glomerulosclerosis	(Zhang et al. 2016)
Rhamnetin	↓miR-34a	↓Notch-1	Non-small cell lung cancercell lines	Inhibition of EMT	(Kang et al. 2013)

↑indicates up-regulated, ↓indicates down-regulated