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Review Article

miRNA as molecular target of polyphenols underlying their biological effects

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ABSTRACT

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

Contents

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

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Introduction

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

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

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

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

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

Impact of polyphenols on miRNA expression

Most studies performed to date have been performed in vitro using native polyphenols at high concentrations rather than metabolites present in the circulation in low concentration, while

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