

## A New Therapeutic Approach to Foods: microRNA

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Geliş / Received: 31/10/2018, Kabul / Accepted: 09/10/2019

### Abstract

With the development of sequencing technology, microRNAs (miRNA) have between 19-24 bases in length which play a role in cell communication was discovered. These miRNAs have important tasks in the development and differentiation of cells, as well as in metabolism. The miRNAs carried in the microvesicle are prevented from degradation depending on the conditions such as extreme pH and temperature. In the current studies, it has been determined that the foods have regulate the activities at cellular level in metabolism by miRNA expression. This was first demonstrated by detecting rice miR-168a which absorbed by digestive system. On the other hand, these miRNAs were found to inhibit the mRNA expression of LDL RAP1 involved in cholesterol transport. In studies where miRNAs have been absorbed by the digestive system, it has been suggested that miRNAs, in particular animal origin, pass into serum and plasma. With the miRNAs have this potential, it can be used as biological markers for the prevention of the health problems associated with diet. It's known that foods contain the components such as fat, sugar, protein, vitamin affect to metabolism not only, but also miRNAs affect it directly or indirectly. A recent dietary miRNA database was created with the increasing importance of foodborne miRNAs and there are miRNA profiles associated with foods such as apples, Atlantic salmon, bananas, chicken meat and egg, corn, beef fat and milk, breast milk, grapes, oranges, pork, rice, tomato, soybeans and wheat in this database. In this study, biosynthesis, the mechanism of action and presence in food and effects on metabolism of miRNAs were discussed.

**Keywords:** microRNA, Food, Disease, Treatment

### Gıdalara Yeni Bir Terapötik Yaklaşım: microRNA

#### Öz

Sekanslama teknolojisinin gelişmesiyle birlikte hücreler arası iletişimde rol oynadığı belirlenen 19-24 bazlık uzunluğa sahip mikroRNA (miRNA)'lar keşfedilmiştir. Bu miRNA'ların insanda hücrenin gelişimi ve farklılaşmasının yanı sıra metabolizmada da önemli görevleri bulunmaktadır. Mikroveziküller içerisinde taşınan miRNA'lar bu sayede aşırı pH ve sıcaklık gibi koşullara bağlı olarak parçalanmaktan korunur. Yapılan güncel çalışmalarda miRNA ekspresyonu ile gıdaların metabolizmada hücresel düzeyde faaliyetleri düzenlediği belirlenmiştir. İlk defa diyetlerine pirinç konularak beslenen farelerde yapılan bir çalışmayla pirinçe ait miR-168a'nın farelerin sindirim sistemi tarafından absorbe edildiği belirlenmiş ve bu miRNA'nın kolesterol transportunda rol oynayan LDLRAP1 mRNA ekspresyonunu engellediği tespit edilmiştir. miRNA'ların sindirim sistemi tarafından absorbe edildiğinin ortaya konduğu çalışmalarda, özellikle hayvansal kaynaklı miRNA'ların serum ve plazmaya geçtiği ileri sürülmüştür. Sahip olduğu bu potansiyel ile miRNA'lar, diyet aracılığıyla ortaya çıkan sağlık problemlerin engellenmesinde biyolojik marker olarak kullanılabilir. Gıdaların sadece içerdiği oldukları yağ, şeker, protein, vitamin gibi bileşenlerinin değil aynı zamanda sahip oldukları miRNA'ların metabolizmayı doğrudan veya dolaylı yollarla etkilediği bilinmektedir. Gıda kaynaklı miRNA'ların önem kazanmasıyla birlikte güncel bir besinsel miRNA veri tabanı oluşturulmuş ve burada elma, atlantik salmon, muz, tavuk, tavuk yumurtası, mısır, sığır yağı ve sütü, anne sütü, üzüm, portakal, domuz, pirinç, domates, soya fasulyesi ve buğday gibi gıdalarla ilgili miRNA profilleri bulunmaktadır. Bu çalışmada miRNA biosentezi, eylem mekanizması ve gıdalardaki varlığı ile metabolizma üzerine olan etkileri tartışılmıştır.

**Anahtar Kelimeler:** microRNA, Gıda, Hastalık, Tedavi

## 1. Introduction

microRNA (miRNA) is a name given to short single-stranded RNAs that are thought to be responsible for the expression of thousands of genes in humans. For the first time in 1993, it was characterized as noncoding RNA from the nematode named *Caenorhabditis elegans*. With the development of sequencing technology, approximately 8,000 miRNAs from humans, including different plants and animals, have been discovered (Ambros, 2004; Bartel, 2004; Howard, K., 2015; Lim et al., 2005). Today, the biogenesis of these miRNAs in human metabolism has been elaborated in detail, and the numerous studies have been conducted on the role of mechanisms in the emergence of diseases. miRNAs regulate the target genes by binding specifically to the target gene transcript in a special way. This is accomplished by promoting the disruption of target RNAs or inhibiting their translation. To date, more than 2,000 miRNAs have been identified that are regulated by the human genome (He and Hannon, 2004; Huang et al., 2011; Sayed and Abdellatif, 2011). However, very few of these have been studied for their functional properties. miRNAs also play a role in stem cell differentiation, apoptosis, and even aging processes. miRNAs produced by cancer cells can be transported to the circulation extracellularly by high density lipoproteins and microvesicles to regulate the organs farther away from the tumor. These microvesicles protect the miRNA from fragmentation of the RNAase and contribute to the transport of the miRNA at long distances. The miRNA profile in healthy and cancerous cells varies. This difference has the potential to be used as a biomarker to predict the outcome of cancer treatment (Chen et al., 2008; Hunter et al., 2008; Kunej et al., 2011; Vrijens et al., 2015).

It is estimated that approximately 60% of the human protein coding genes contain miRNA binding sites. In view of this prediction, miRNAs seem to play a prominent role in metabolic disorders such as obesity and diabetes. It is known that vitamin and secondary plant metabolites affect cellular processes by regulating miRNA expression (Bartel, 2009; He and Hannon, 2004; Maciotta et al., 2013). Zhang et al. (2012) reported that they found miRNAs of rice in serum and tissues of mice which received rice in their diet. It has also been found to miR-168a of rice in the serum of these mice. miR-168a is a type of miRNA that reduces the amount of LDLRAP1 protein present in the liver, thereby increasing the level of LDL. In the same study, compared with the control group, mice in the experimental group detected more LDL than those in the control group. This suggests that the increase in the level of MIR168a, which was transmitted through the plant, resulted in a decrease in LDLRAP1 protein and therefore an increase in LDL. The same researchers have suggested that plant miRNAs in food are then packaged again into microvesicles and taken up into the intestinal epithelial cells and left in the circulatory system. However, the basic mechanism for the absorption of miRNAs has not been clearly demonstrated. Despite the sensitivity of RNAs to extreme conditions, the high stability and resistance of miRNAs to RNAase activity, as well as their resistance to a wide range of temperature and pH, partly explain their passage from the gastrointestinal tract. This information suggests that miRNAs can be used for therapeutic purposes. Along with the mentioned work, researchers have focused on the study of the migration of miRNAs in diet to human beings. Changes in the decrease and increase in the level of miRNA in the genome will depend on the transfer between the species, and the

determination of the relationship of the different gene regions with the exocycle will be a major current approach in this regard. In this review, biosynthesis of miRNAs, their activity at cellular level, and studies on miRNAs found in green were investigated.

## 2. Biosynthesis of miRNA

Some of the miRNAs are encoded in their own genes while others are encoded in sequences as part of the host-protein encoding genes. According to the gene patterns, miRNAs are categorized into two groups: "intergenic miRNAs" encoding the localized miRNAs between protein-encoding genes and "intragenic miRNAs" localized within the host protein encoding genes. miRNAs are classified in this way with the length of 19-24 bases. The first step of miRNA synthesis begins by transcribing as the first long transcript by RNA polymerase II or RNA polymerase III, called primer miRNAs (pri-miRNAs). Following the transcription of the miRNA genes, the post-transcriptional process begins. pri-miRNAs are transformed into precursor miRNAs by RNase endonuclease III Droscha and partner DGCR8/Pasha (Creugny et al., 2018; Cullen, 2004; Esau and Monia, 2007; Hwang and Mendell, 2006; Montecalvo et al., 2011; Valadi et al., 2007). Introns containing precursors turn into mirtrons. Thus, formed pri-miRNAs are transported to cytoplasm from nucleus via nuclear pores by Ran GTP and exportin-5. The pri-miRNAs in the cytoplasm are cleaved to form the mature miRNA/miRNA duplex with ~22-nt length by the RNase III enzyme, called Dicer. The resulting mature miRNAs are integrated into the RNA-induced silencing complex to form the miRNA:RISC (miRISC) complex. Only one of miRNA/miRNA chain is adhered to the RISC while the other is eliminated. In

this way, miRNAs with functional properties are involved in action mechanisms (Calin et al., 2004; Franco-Zorrilla et al., 2007; Gomes et al., 2017; Megraw et al., 2007; Pedersen et al., 2007; Weiss and Ito, 2017).

## 3. Mechanism of Action of miRNAs

miRNA/double-stranded RNA (dsRNA) shows activation in miRISC complex system. A miRNA in miRISC is connected to the untranslated 3' (3' UTR) of the mRNA targeted by the Watson Crick base-pairing mechanism with the fully complementary 5'-end 2-8 nts to identify the motif in the target. The complex formed on the 3' UTR of miRNA/RISC affects the protein production either by increasing the deadenylation or suppressing the initiation of translation, or both. The higher degree of complementarity of accessible binding sites, the more mRNA targeted by miRNA is fragmented (Cai et al., 2009; Gu et al., 2009; Gulyaeva and Kushlinskiy, 2016; Manning and Cooper, 2017; Wahid et al., 2010)

## 4. Food-borne miRNAs

MiRBase (<http://www.mirbase.org/>), TargetScan ([http://www.targetscan.org/vert\\_72/](http://www.targetscan.org/vert_72/)), Miranda (<http://www.mirtoolsgallery.org/miRToolsGallery/node/1055>), and MirTarBase (<http://mirtarbase.mbc.nctu.edu.tw/php/index.php>) are online archives where contain the miRNAs and target regions. The most important of these is miRBase, which contains data of 64.473 miRNAs isolated from 223 species. Database (DMD) was created by Chiang et al. (2015) for researching and analysing the relationships between dietary-specific miRNAs and human health-diseases. In this page, there

are miRNA profiles related to foods such as apple, atlantic salmon, bananas, chicken eggs, corn, cattle oil and milk, breast milk, grape, orange, pig, rice, tomato, soybean

meal and wheat (Figure 1). Currently, 5,217 miRNAs of nutritional origin are found in this database. Researchers can upload data about miRNAs to database.

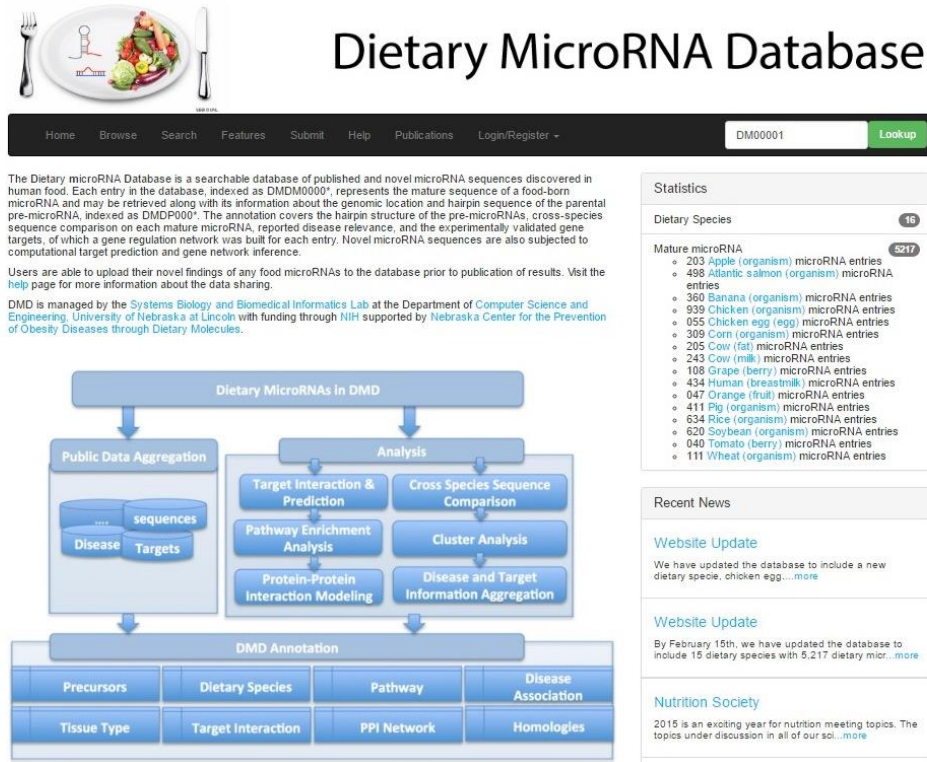


Figure 1. Diet-based miRNA Database (<http://sbbi-panda.unl.edu:5000/dmd/>)

## 5. The Presence of miRNAs on Foods and Effects on Metabolism

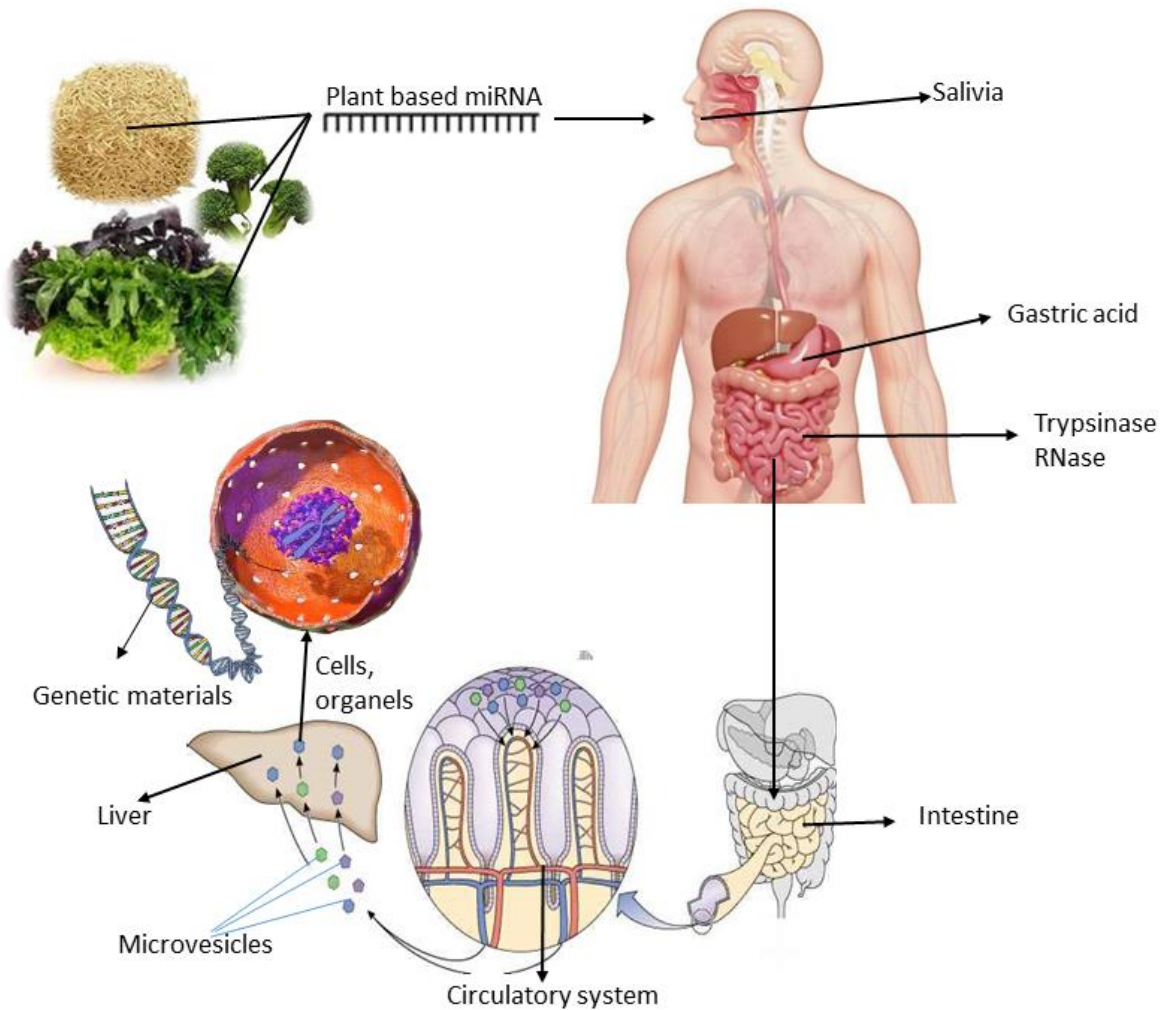
Unlike animal origin miRNAs, bioavailability of plant-derived ones by the body is a controversial issue. Animal origin miRNAs are more likely to survive under the extreme conditions of the digestive system and pass through the intestinal barriers. The ability of these miRNAs to be protected from environmental conditions is possible by transporting them in extracellular vesicles. Exosomes, which are important in extracellular vesicles, have different surface proteins that affect cellular uptake of both animal-derived and plant-derived miRNAs (Farmer and Hirschi,

2017; Liang et al., 2015; Lukasik and Zielenkiewicz, 2017; Meng et al., 2011; Wang et al., 2018). However, since the structure of these surface proteins is different, plant-derived miRNAs are adversely affected by the intestinal cells (Wagner et al., 2015). Studies have shown that miRNAs in consumed foods regulate the directly expression of endogenous genes. The probable pathway of the plant-derived mirnas in human metabolism is given in Figure 2.

In a study carried out by Zemleni et al. (2015) found that milk-borne miRNAs are absorbed by intestinal system of humans. This study showed that absorbed miRNAs had changed the gene expression of human leukocytes in cultured kidney cells and rat liver. It has been reported that miRNA

called miR-29b changed the expression of RUNX2 and regulated the gene expression as a bioactive food component with this activity. The same researchers investigated that miRNA-181a and miR-181b at the molecular level to examine whether egg-borne miRNAs caused the changes in gene

regulation in the human body. It has been reported that miR-181b present in plasma was 150% higher than normal at 9 hours following egg consumption, whereas miR-181a, not normally found, was detected in red blood cells at 154% higher level than normal level.



**Figure 2.** The probable pathway of the plant-derived miRNAs in human metabolism

Quercetin is a polyphenolic compound found in certain fruits and vegetables, and in an epidemiological study, it was found that this substance reduced the incidence of lung cancer. Lam et al. (2012) reported that the let-7 family, known as tumor suppressors, up-regulated with frequent quercetin-rich food intake. Similarly, they also found that levels of miR-146, miR-26 and miR-17, which also play a role in

carcinogenesis, strongly up-regulated in individuals who consumed quercetin rich diet.

Breastmilk is an important foodstuff that is known to play a key role in the feeding and development of infants. There is also activity in infants that leads to the formation and sustainability of the immunity system. Kosaka et al. (2010) reported that immune-

related miRNAs in the mother's milk during the first 6 months of lactation were expressed at higher levels. At the same time, they suggested that these miRNA molecules were even more resistant to acidic conditions and that miRNAs could be taken by infants through the diet. In this study, it was determined that breastmilk had an effect that regulate the development of the baby's immunity system by miRNAs. In another study (Baier, S. and Zemleni, 2014), miR-29b, found in the cow's milk, was taken with the diet and found to be altered in terms of expression in human genes. It was reported that these miRNAs which have an important place in terms of bone health were 247% more expressed at the end of 3 weeks in the milk-fed individuals. This study revealed that a significant relationship between miRNA content of foods consumed by humans and potential effects on health. Raw cow's milk is presented to the market after it has gone through various stages of process. In a study (Howard, K. M. et al., 2015) to determine the level of miRNAs in raw milk affected by these processes, pasteurization and homogenization were found to cause a loss of 63% at the miR-200c level and 67% at the miR-29b level. It was suggested that a 40% loss in miR-29b level in microwave heating, even though the effect of cold storage and somatic cell counts remained low. These results have shown that the amount of highly stable miRNAs may be reduced following various practices. Baier, S. R. et al. (2014) reported that miR-29b and miR-200c in the milk were absorbed at a high level. The RUNX2 factor targeted by miR-29b was found to a 31% increase in mononuclear cells with milk consumption. In the same study, miR-29b was found to be expressed in 61% less in tissues of mice fed the miRNA-poor diet compared to in tissues of mice fed diets with normal miRNA levels for 4 weeks.

Fruit and vegetable polyphenolic compounds are known to play an important role in eliminating chronic inflammation, especially colon cancer, by anti-inflammatory effects. As a result of a study by Angel-Morales et al. (2012) to demonstrate the relationship between red wine extract polyphenolic compounds and miR-126, it was reported that these compounds reduced mRNA expression of lipopolysaccharide-induced NF-KB, ICAM-1, VCAM-1 and PECAM-1. This result has been shown to polyphenolic compounds obtained from red wine have an anti-inflammatory potential effect on CCD-18Co myofibroblast cells by affecting miR-126 level.

Recent studies have shown that foodborne miRNAs affect the level of miRNA expression in the genome and thus have implications for fatal diseases such as cancer. As is known, food items such as folate, selenium, fatty acids have preventive effects on the development of cancer. Various studies have been carried out to determine the effects of these nutrients on the development of cancer by directly or indirectly affecting miRNA expression. In another study (Kutay et al., 2006), hepatocellular carcinoma was detected at 54-week in rats fed a methylene-poor diet. In mice fed normal diet compared to mice fed the methylene-poor diet, levels of let-7a, miR-21, miR-23, miR-130, miR-190 and miR-17-92 increased while miR-122 expression levels decreased. However, miR-122 returned to normal level when the methyl-deficient diet of mice was converted to methylated diet after the 36th week, no cancer development was reported.

## 6. Conclusion

Studies continue to reveal the potential effect of miRNA on fetal development and growth. This have been acquired a new perspective on the therapeutic uses of foods

that are thought to play an important role in this regard. It will be come a long way in terms of public health with new studies on this issue which will contribute to the elimination of important problems of our time, such as obesity, hepatic disorders, diabetes, cardiovascular system diseases and cancer. With the new therapeutic approaches, the changing of miRNAs in the foods will lay the groundwork for the emergence of new technological initiatives by companies that produce the foods.

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