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Review

Dietary microRNAs (miRNAs) and Their Cutting-Edge Use in Food Science

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Abstract: Food quality and dietary habits have a significant impact on human health. Growing evidence suggests that miRNAs have been extensively detected in various dietary sources, including plants and animals. miRNAs are a class of small non-coding RNA that regulates gene expression in a sequence-specific manner and modulates various biological processes. These dietary miRNAs are transported through the circulatory system and affect the expression of the gene in the recipient cells through a process called cross-kingdom regulation of the gene. This review will provide insight into the role of dietary miRNAs, their stability and transport mechanisms, as well as their impact on human health. Likewise, we update and discuss the future consequences of dietary miRNAs and their possible use in the treatment of various human diseases.

Keywords: gene regulation, miRNA, dietary miRNAs, cross-kingdom, cross-species, therapeutics

1. Introduction

Food safety and health are considered to be the most important aspect of life in higher living organisms, including humans. As a result, these are the major global concerns that are primarily caused by inadequate nutrition or tainted food. Recent evidence suggests that food alters gene expression and its regulators, such as miRNAs and transcription factors (TFs) [1-3]. miRNAs are a class of non-coding endogenous small RNAs that have been shown to have a crucial role in gene regulation and various biological processes, including plants and animals [4-10]. In addition, miRNAs can work cross-species and regulate the biological function both intracellularly and intercellularly [7, 11-12]. These miRNAs also help in plant-plant interactions for instance, *Cuscuta campestris* (*C. campestris*) can accumulate 22-nt miRNAs in its haustoria and transport them to their host plants to silence the host genes and facilitate *C. campestris* growth during parasitism [7, 13]. Further research on *Arabidopsis-Botrytis cinerea* (*B. cinerea*) interaction revealed that

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the host *Arabidopsis* cells secrete extracellular vesicles that resemble exosomes to transport sRNAs into the *B. cinerea* to suppress their pathogenicity by silencing fungal virulence genes [7, 13].

Furthermore, it has been reported that plant-derived Exosome-like nanoparticles (ELNs) that contain ginger miRNAs such as mdo-miR7267 are taken up by the gut microbiota *Lactobacillus rhamnosus* that alter microbiome composition and host physiology [7, 14]. Zhang and his co-worker demonstrated the first evidence of cross-kingdom regulation of miRNAs. Further, they showed that miR168a, a typical plant-derived miRNA highly abundant in rice, was able to bind the mRNA of *Low-density lipoprotein receptor adaptor protein 1* (*LDLRAP1*) in mammalian bodies and decreased the clearance of LDL from the blood [15]. These results suggested that exogenous plant miRNAs in food can control the expression of mammalian genes. However, several other studies, which were carried out during the same period as Zhang's study, have failed to provide evidence of such a transfer between species. Dickinson and colleagues challenged Zhang's hypothesis in 2013. They showed no evidence of intake of consumed plant miRNAs by mice or any reduction in *LDLRAP1* levels in mice's liver [16]. Further, Witwer and his co-worker also obtained similar results, implying that their findings do not support the general and consistent uptake of plant dietary miRNAs [17]. Later, in 2013, Chen and colleagues argued that the difference in outcomes could be attributable to nutritional inequalities in the diet ingredients [18]. They also argued that the sequencing approach used by Dickinson et al. might not be capable of effectively measuring plant miRNAs [18]. After Writer and Chen, Kang and colleagues also did a comprehensive meta-study on xenomiRs and perform feeding trials on rats and piglets. Surprisingly, they also have not found any plant miRNAs in rat blood or bovine milk sequences in piglet blood [19]. Later, some research indicated that the exogenous miRNAs from food/dietary sources can be absorbed through the gastrointestinal tract (GIT) and delivered into cells, where they can regulate gene expression and other biological processes [7]. Recently, in miR144/451 null mice has been demonstrated that the ingestion of miR451 rich diet can increase the concentration of miR451 in the circulating blood and boost the antioxidant capacity of red blood cells (RBCs). Moreover, lowering the level of miR451 curtails the antioxidant capacity of miR-144/451 null RBCs by the 14-3-3Z/Forkhead box O3 (FOXO3) pathway [7, 20].

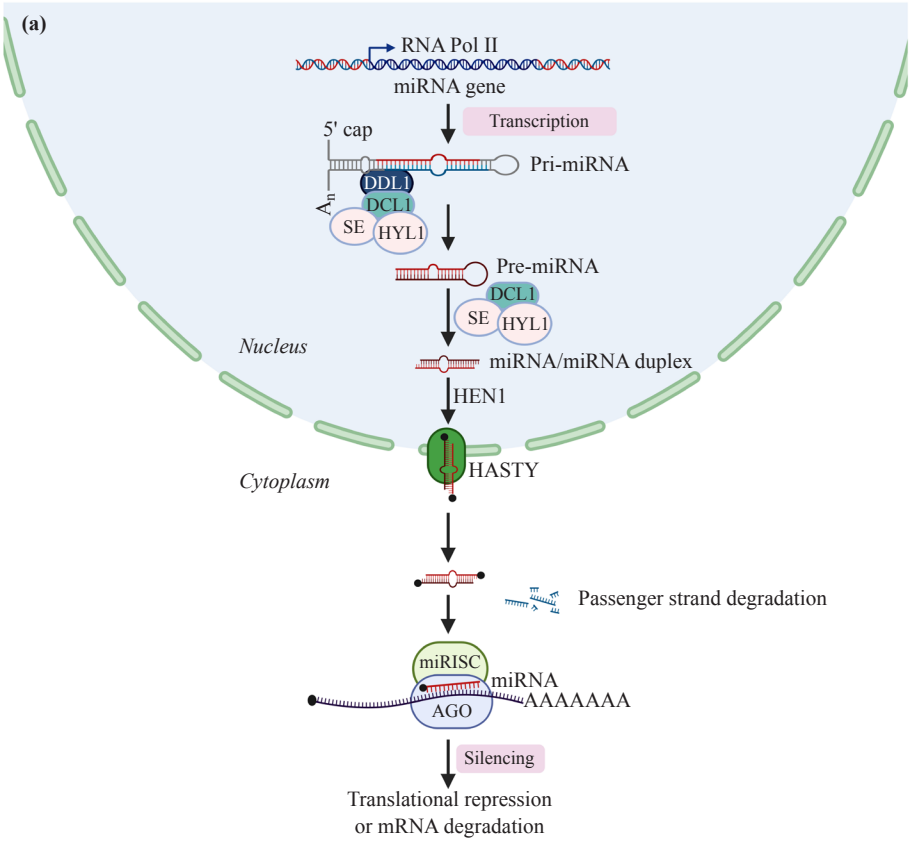
miRNAs regulate the expression of the target gene at post-transcription as well as a translational level [3, 21-24]. As a result, it is predicted that more than 60% of human protein-coding genes have at least one conserved miRNA binding site as well as various non-conserved sites [25]. Thus, dietary miRNA may play an important role in various biological and developmental processes such as apoptosis, metabolism, immunological responses, hormone signalling, cell proliferation, differentiation, etc. [25]. Moreover, miR162a found in the larval diet has been shown to directly target *Apis mellifera Target of rapamycin* (*amTOR*) to govern honeybee caste development, providing insights into cross-kingdom interaction and co-evolution [7, 26]. Previously, 1400 miRNAs were identified in milk using diverse molecular biology techniques [27]. Recently five plant-derived miR156a, miR157a, miR166a, miR168a, and miR172a, were identified to be present in breast milk [28]. These miRNAs are considered to be a nutritious component of milk that regulates developmental outcomes in the infant organism. The rapeseed (*Brassica campestris*) miR159 and miR166a were detected in mice blood which was absorbed by mice during feeding [29]. These dietary miRNAs have been investigated as a potential therapeutic agent for the treatment of various disorders/diseases such as inflammation, autoimmune responses and cancer [3, 7, 25, 30-33]. Furthermore, several studies have shown the mutual regulation of miRNAs and nutrition. It has been recently reported that miRNAs play important role in regulating nutrient metabolism, including hepatic insulin sensitivity, cholesterol, and lipid metabolism [1, 29]. Thus, emerging data indicated that these dietary miRNAs could be considered a novel functional component of food that can be exploited as a therapeutic agent in the treatment of various genetic and non-genetic diseases.

In this review, we discuss the current understanding of dietary miRNAs based on numerous studies and the mechanism of cross-kingdom regulation of dietary miRNAs as well as their potential uses as a therapeutic agent against various diseases/disorders. In addition, we will briefly summarises the regulatory effects of miRNAs on gut microbiota and host cells, and how they are beneficial to health. We aim to present a preliminary analysis of studies to aid in the therapeutic development of dietary miRNAs. This review will provide a new perspective on the role of dietary miRNAs in the treatment of various human and animal diseases.

2. miRNA biogenesis in plant and animal system

miRNAs are a class of 21-24 nucleotides (nt) non-coding RNAs that are ubiquitously present in both plants

and animals [3, 21-22, 24]. It has been shown that miRNAs control the expression of their target gene at the post-transcriptional through complementary base pairing [3, 21-22, 24]. Although there are some similarities between plant and animal miRNAs, in contrast, there are also notable distinctions in terms of their biogenesis, mechanism of action, and evolution [3, 21-22, 24]. In both systems, mostly the miRNAs are first transcribed by RNA polymerase II (RNA pol II) into primary miRNAs (pri-miRNAs) with a 5' cap and 3' polyA tail. These pri-miRNAs are further processed into precursor miRNAs (pre-miRNAs) by multiple protein complexes known as microprocessor complex enzymes [3, 21-22, 24]. In the plant system, this is accomplished by a complex of proteins including Dawdle (DDL), Dicer-like1 (DCL 1), Serrate (SE), and Hyponastic leaves1 (HYL1), whereas in the animals' system, it is carried out by a DiGeorge syndrome critical region 8 (DGCR8) and Ribonuclease III (RNase-III) family enzyme Drosha (Figure 1a and 1b) [3, 21-22, 24, 34-35]. In plants, these pre-miRNAs were then processed in the nucleus by the DCL1, SE, and HYL1 proteins into miRNA-miRNA* duplex [22, 36-37]. These duplexes are further methylated by the HEN1 protein and exported to the cytoplasm with the help of exportin protein including HASTY [3, 21-22, 24]. The one strand of the duplex is then loaded into an Argonaute 1 (AGO1) containing miRNA-induced silencing (miRISC), which further regulates the expression of target gene(s) by complementary base pairing (Figure 1a) [3, 21-22, 24]. In animals, however, the nuclear pore complex (NPC) transports pre-miRNAs to the cytoplasm with the help of Exportin 5, which requires the RanGTP as a co-factor (Figure 1b). This pre-miRNA is further processed into miRNA-miRNA* duplex in the cytoplasm by protein complexes that include DICER, Transactivating response RNA binding Protein (TRBP), and protein activator of Protein kinase RNA (PACT) [35]. The duplex is subsequently loaded into the AGO protein within RISC, where one strand is preferentially maintained [35]. Further, this complex is coupled with the GW182 protein, recognizes its target gene(s), and inhibits protein synthesis (Figure 1b). Despite the main differences in their biogenesis in both plants and animals, the plant miRNAs control the expression of their target gene(s) through either transcript cleavage or translational inhibition via extensive base pairing with the target gene(s). However, in animals, miRNAs undergo hybridization between their 'seed' sequence (mostly positions 2-8) and target gene(s) leading to translational inhibition, mRNA degradation, and in certain cases translation activation or increased RNA stability [35, 38-40].



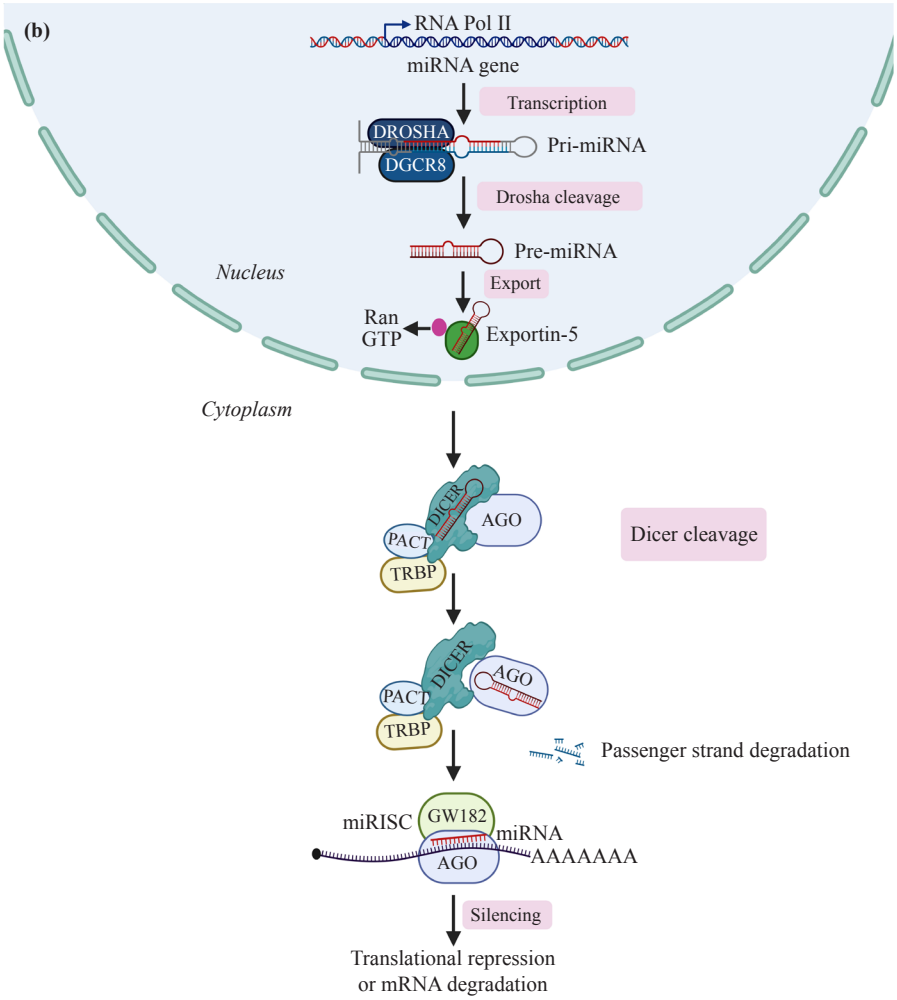


Figure 1. miRNA biogenesis in the plant and animal system. (a) miRNA biogenesis in the plant system, and (b) miRNA biogenesis in an animal system.

3. Dietary miRNAs

miRNAs have been found in a wide range of dietary sources, including plants and animals [30-31]. The uptake of such exogenous miRNAs from a dietary source, which further affects the expression of the gene in the recipient cells known as miRNAs mediated cross-kingdom regulation of the gene [41]. The first evidence of cross-kingdom transfer of functionally active miRNAs was reported by Zhang et al. in 2012. In this study, the rice miR168a has been shown to inhibit *LOW-DENSITY Lipoprotein receptor adapter protein 1* (*LDLRAP1*) and thereby decreases LDL removal from human/mouse plasma [15]. Dietary miRNAs have unique characteristics in terms of their stability, absorption, transport, and functional mechanisms [7, 42]. However, there is still a significant lack of mechanistic nous into these aspects of dietary miRNA, and further research is needed to answer all of these questions [7]. Recent research has demonstrated that both plant and animal miRNAs can be absorbed and act within recipient organisms and regulate their biological functions by modulating target gene(s) [7]. The *Populus euphratica* miRNA, peu-miR2910, which is conserved in fruits and vegetables, was found to be present in higher concentrations in human plasma compared to other detected human miRNAs. In certain samples, up to a thousand copies of peu-miR2910 were detected, which was more abundant than the rest of the human miRNAs detected [43]. According to recent investigations, maize, melon, sorghum, tomato, tea, and oil palm are potential sources for miR2910, indicating the evidence that this miRNA reached human plasma through food ingestion [3, 43]. Furthermore, miR2910 has been predicted to potentially target human Janus kinase (JAK)-

Signal transducer and activator of transcription (STAT) signalling pathway gene *Sprouty RTK signalling antagonist 4* (*SPRY4*), and 5' untranslated region (5' UTR) of *LIM domain and actin binding 1* (*LIMA1*), and the coding DNA sequence (CDS) of *Catenin delta-1* (*CTNND1*), *Folate-receptor 1* (*FOLR1*), *Ladybird homeobox 1* (*LBX1*), *Serine/threonine-protein kinase 38* (*STK38*), *Family with Sequence Similarity 127, Member B* (*FAM127B*), *Plant homeodomain* (*PHD*) *finger protein 19* (*PHF19*), *Human zinc finger protein 295* (*ZNF295*), and *Mitochondrial ribosome recycling factor* (*MRRF*) genes, indicating it may be use in the treatment of various human diseases [3, 43-44]. To date, numerous dietary miRNAs have been identified for their potential roles in the treatment of various human diseases. Recently, computational studies showed that *clo*-miR14 from *Curcuma longa* exhibits cross-kingdom regulation. Further, the authors showed that *clo*-miR14 was stable in mammalian serum for a prolonged period and predicted to target various inflammation-related genes that have an important role in human rheumatoid arthritis [45]. As a result, clo-miR14 could be a promising candidate for the treatment of rheumatoid arthritis in the near future [3]. Recently, miR159 from *Arabidopsis*, soybean, and broccoli have been shown to be effective in the treatment of mice breast cancer [3]. In the medicinal plant kingdom, a large number of miRNAs have been identified that can be used to treat various human diseases, including cancer [46-47]. As we mentioned above milk is a rich source of nutrition. Recent research indicates the presence of miRNAs in milk, increasing its significance in medical biology. Recently, 602 miRNAs have been identified in human breast milk exosomes by using deep sequencing technology [48]. These exosomal miRNAs have been demonstrated to be resistant to prolonged room temperature, RNase digestion, multiple freeze-thaw cycles, and even boiling [48]. Furthermore, the authors hypothesized that these exosomal miRNAs are movable from the mother to the infant's body and may have a potential role in the development of the infant's immune system [48]. Lately, colostrum microvesicles (MVs) have been shown to contain various immune-related miRNAs, which may have a significant role in immune response [49]. Further studies have shown that these MVs are crucial for the immunological regulation and transmission of miRNA [49]. Recently, microarray analysis shows that the milk miR22-3p regulates gene expression in Human intestinal epithelial cells (HIECs). These microarray data were then validated using qRT-PCR of selected genes, including *CCAAT/enhancer-binding protein* δ (*C/EBPδ*), *Tumor protein p53 inducible nuclear protein* (*TP53INP*), Tetratricopeptide repeats 3 (*IFIT3*), *Interferon-induced protein with tetratricopeptide repeats 1* (*IFIT1*), and *C-X-C motif chemokine 10* (*CXCL10*). The functional examination of the modified genes showed that miR22-3p played a crucial role in cell proliferation, immune function modulation, and apoptosis inhibition. As a result, miR22-3p acts as both a tumour suppressor and an oncogene [50]. Previously, some miRNAs have been detected in bovine milk exosomes [51]. Recently, miR30-5p, miR125b, miR148a-3p, miR181d, miR200c-3p, let7a-5p, miR21-5p, and miR223 were identified in extracellular vesicles from bovine milk or in milk from other species [52-53]. These milk-derived miRNAs have been shown to be potentially involved in the regulation of innate immunity, growth and development, cell proliferation, and apoptosis [51, 53]. Moreover, several miRNAs have been identified in human breast milk (HBM) that may have a potential role in the treatment or prevention of major human diseases like cancer and neurological disorders [54-55]. Recently, HBM-derived exosomal miR148a-3p has been shown to protect against Necrotizing enterocolitis (NEC) by controlling *p53* and *Sirtuin 1* (*SIRT1*) [56]. It has been shown recently that exosomal miRNAs such as let7, miR29, miR223, and miR103, can control diabetes [53]. Recently, plant polyphenols have been identified as a potential treatment approach for diabetes and cancer [57-60]. These plant polyphenols can be found in various foods, including tea, coffee, beans, apples, berries, citrus fruits, wine, plums, broccoli, chocolate, and herbs [59-60]. Serval reports have been indicated that numerous miRNAs were differentially altered in diabetic and cancer-affected patients [58-59, 61]. These polyphenols act by modulating the expression of miRNAs, which in turn affects the expression of their target gene(s). Dietary polyphenols such as Chlorogenic acid (CGA), Curcumin (CUR), and Epigallocatechin gallate (EGCG) have been shown to downregulate the tumor-promoting miR21 [59]. Moreover, CUR, EGCG, and Resveratrol (RSV) can induce tumor-suppressing miR16, miR34a, miR145, and miR200c while reducing tumor-promoting miR25a [59]. Literature scan on recent studies have indicated that CGA, EGCG, and RSV downregulated the tumor-suppressing miR20a, miR93, and miR106b [59]. In addition to cancer, these polyphenols have been demonstrated to protect against diabetes complications by altering the expression of miRNA(s) in human tissue/cell [58]. RSV has recently been found to protect diabetic cardiomyopathy, retinopathy, and neuropathy by altering the expression of miR15, miR21, miR30c2, miR34a, miR126, miR155, miR181b, and miR663 [58]. Furthermore, miR146a from *Prunus spinosa* L. fruit has been shown to play a vital role in diabetic wound healing [58]. Thus, these findings suggest that dietary miRNAs may act as a new biologically active component that is absorbed into animals via the GIT and affects their physiological and

pathological responses.

4. Transport and stability of dietary miRNAs

In addition to competing theories about the stability of dietary miRNAs and how dietary miRNAs can regulate gene expression across kingdoms, concerns have also been raised about how these molecules can cross the GIT, enter the bloodstream, and move from cell to cell. To address all of these concerns, researchers have conducted additional research on the cross-kingdom communication of dietary miRNAs. These dietary miRNAs are acquired through diet and absorbed in the GIT (Figure 2) [3, 30-31]. According to emerging evidence, these dietary miRNAs can be secreted into extracellular fluids and transported to target cells in three different ways: (I) active secretion via exosomes vehicles (EVs) or microvesicles (MVs) (II) active secretion via RNA binding protein including Argonaute 2 (AGO2), High-density lipoprotein (HDL), Nucleophosmin 1 (NPM1), etc. and (III) passive secretion from broken or damaged cells caused by tissue injury, inflammation, cell necrosis or apoptosis [30-32, 62-64]. Further research has been conducted on the cross-kingdom trafficking and stability of dietary miRNAs [7, 41, 44, 47]. It has been observed that dietary miRNAs can survive in the mammalian circulatory system under adverse conditions such as low pH, bowel movements, and RNase treatment. Furthermore, these dietary miRNAs were found to be stable during food processing, cooking, and digestion [7, 41, 44, 47].

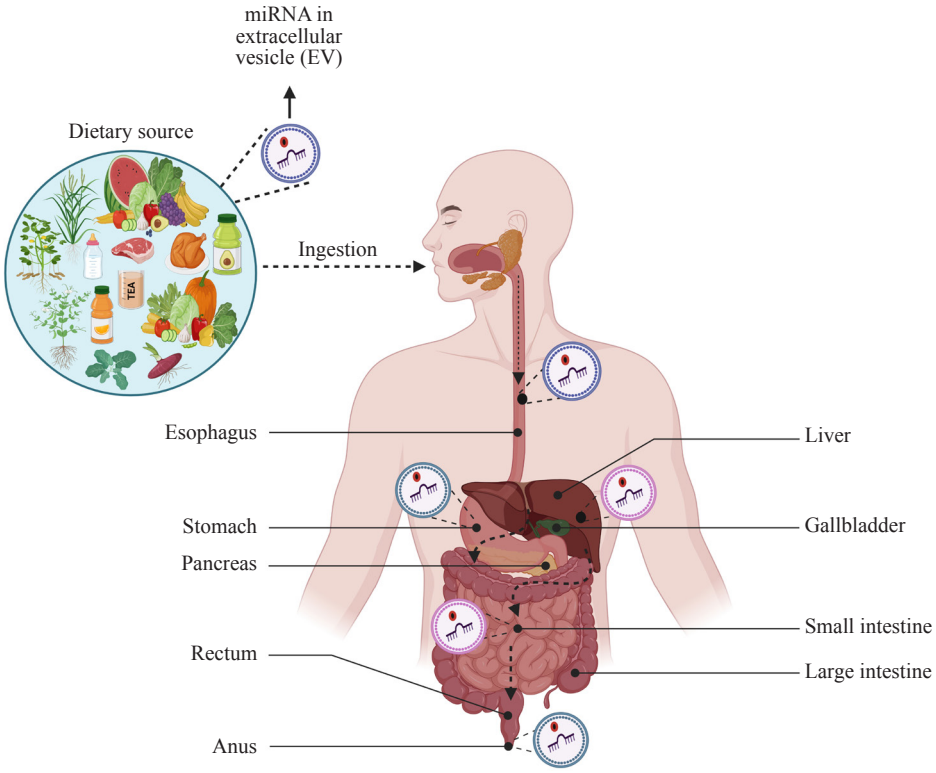


Figure 2. Diagram depicting the route and uptake of dietary miRNAs into human cells. These miRNAs are found in dietary sources naturally. Following meal consumption, these dietary miRNAs pass through different barriers such as RNases, acidic pH digestive enzymes, degradative enzymes, etc. throughout the GIT before reaching the circulatory system. Afterwards, these miRNAs are transferred from cell to cell to a specific cell or tissue where they regulate their target gene(s) expression.

5. Therapeutic use of dietary miRNA

Although the significance of exogenous miRNAs in the mammalian system is not yet fully understood, the biological impacts of dietary miRNAs in the mammalian system have been studied using computational or bioinformatics tools. However, the ability of miRNAs in cross-kingdom regulation of gene expression indicates that dietary miRNAs may have therapeutic applications [65-66]. Interestingly, these dietary miRNAs have developed into prognostic biomarkers for the diagnosis and prognosis of diseases like cancer, epilepsy, viral infections, neurological illness, cardiovascular disorders, sepsis, diabetes, and muscular disorders [65-68]. Numerous studies have been reported to determine how dietary miRNAs contribute to the treatment of various human/animal diseases [7, 33, 47, 65-66, 69-73]. Recently dietary miRNAs have been implicated in the treatment of various genetic and non-genetic diseases/ disorders in humans (Figure 3, Table 1). [3, 14, 74-78]. Some current knowledge and the application of dietary miRNAs in the mammalian systems are presented in (Figure 3 and Table 1).

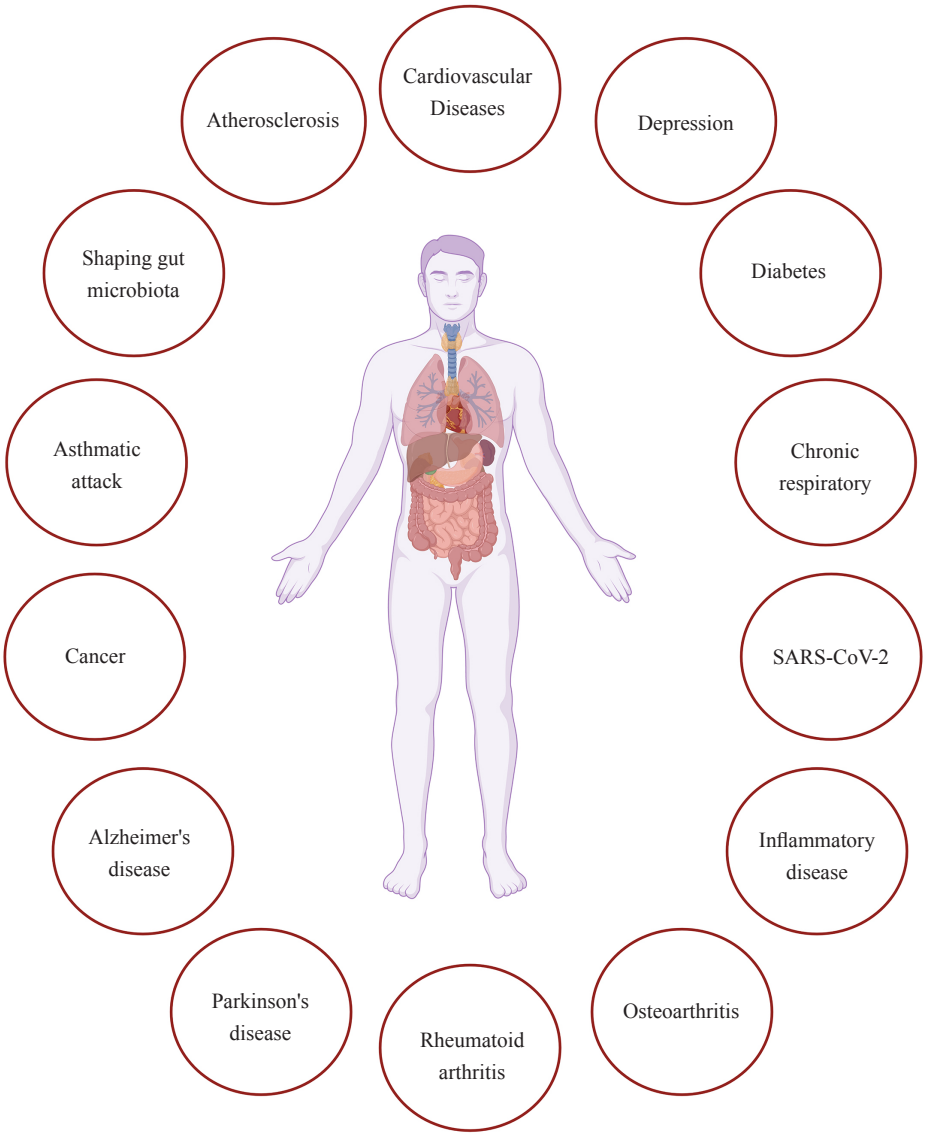


Figure 3. Application of dietary miRNAs in the treatment of various diseases in humans

Table 1. The therapeutic use of dietary miRNAs in the treatment of various diseases

	miRNAs	Source	Target gene	Target Organism/Cell	Therapeutic Applications	References
1	miR156a	Green veggies	*Junction adhesion molecule-A* (*JAM-A*)	Human/HAEC cells	Reduces risk of Atherosclerosis	[41, 79]
2	miR159	*Arabidopsis thaliana*, *Glycine max* (*G. max*), Broccoli	*Transcription factor 7* (*TCF7*)	Mice/breast cancer cells	Suppressed the growth of xenograft breast cancers.	[41, 80]
3	miR168	*Oryza sativa*	*Low-density lipoprotein receptor adaptor protein-1* (*LDLRAP1*)	Human, Mouse, Rat, Calf, Hoarse, Sheep	Regulate LDL level	[15, 41, 66]
4	miR146a	Plant-chow diet	*Tumor necrosis factor receptor-associated factor 6 (TRAF6), Interleukin-1 receptor-associated kinase 1 (IRAK1)*	Mice	Listeria monocytogenes	[81]
5	miR7267-3p	Ginger	*Lactobacillus rhamnosus (LGG) monooxygenase ycnE*	Mice	Antimicrobial immunity and tissue repair in mice	[14, 70]
6	miR6300	Ginger, grapefruit	*Open reading frame 3a (ORF3a)*	SARS-CoV-2 genome	Treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	[73]
7	miR5754	*Medicago truncatula*	*Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1)*	Human colorectal carcinoma HCT116 cell line	Cancer treatment	[82]
8	miR4995	*G. max*	*Nuclear paraspeckle assembly transcript 1* (*NEAT1*)	Human colorectal carcinoma HCT116 cell line	Cancer treatment	[82]
9	miR2911	Honeysuckle	*Polymerase proteins (PB2), Influenza a virus nonstructural protein 1 (NS1)*	Influenza A viruses (IAVs)	Inhibits virus replication	[41, 83]
10	miR29b	Cow derived milk	*Runt-related transcription factor 2* (*RUNX2*)	Human, Mice	Cancer treatment	[66, 84]
11	miR200c	Cow derived milk	*Zinc finger e-box binding homeobox 1 (ZEB1)*	Human, Mice	Cancer treatment	[66, 84]
12	miR22-3p	Colostrum	*C/EBPδ*	Human	Cancer treatment	[50, 85]
13	miR106a	Colostrum	*Interleukin 10* (*IL-10*)	Macrophage celll line RAW264.7	Immunity	[49]
14	miR451	Colostrum	Macrophage *migration inhibitor factor* (MIF)	Macrophage celll line RAW264.8	Immunity	[49]
15	miR181a	Colostrum	*Caudal-related homeobox 2* (*CDX2*), *GATA6* and *NLK*	Macrophage celll line RAW264.9	Immunity	[49, 86]
16	miR148a-3p	HBM	*p53* and *SIRT1*	Human	Necrotizing enterocolitis	[56]

6. Conclusion and future perspectives

Humans' diets have changed as a result of increased global development, posing new health challenges. However, the discovery of cross-kingdom regulation of gene expression by dietary miRNAs suggests a novel approach that could be used as a potential therapeutic tool to treat various genetic and non-genetic diseases. Thus, this finding has led to the idea that functional miRNAs could be produced from dietary sources by using bioengineering, in addition to plant-derived therapeutic miRNAs. Although dietary miRNAs are widely used to treat many diseases. However, several challenges must be surmounted before therapeutic miRNAs can be used routinely in clinical trials, such as an effective method for directing therapeutic miRNAs to their target cells in vivo, a protected delivery method, efficient uptake of miRNAs by target cells, the risk for genomic integrations etc. We hope that these challenges can be distinctly identified

and specifically addressed.

Author contribution

VM designed the outline of the article. VM and PKP wrote the manuscript (MS) and designed the figures. PKP, JS, and VV provided scientific feedback and critical comments. VM, PKP, JS, VV, PS, and BM revised and edited the MS. All the authors read and approved the MS.

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Conflict of interest

The authors declare no competing financial interest.

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