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Research Article

The evolutionary relationships of microRNAs in the regulation of glucose and lipid metabolism in human and animals

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ABSTRACT

microRNA (miRNA) is a non-coding RNA type, regulating gene expressions at a post-transcriptional level. Changes in miRNA expressions can cause problems such as lipid metabolism disorder, cardiovascular disease, growth retardation, low birth weight and insulin resistance, etc., in human and animals. In this study, we investigated the evolutionary relationships of 14 miRNAs including hsa-miR27a-5p, hsa-miR149-3p, hsa-miR374c-5p, mmu-miR-678, mmu-miR-698-5p, hsa-miR-199a-3p, hsa-miR122-3p, hsa-miR342-3p, mmu-miR201-5p, hsa-miR429, hsa-miR370-3p, hsa-miR130a-5p, hsa-miR330-3p and hsa-miR770-5p related to different metabolic pathways including cardiovascular diseases and lipid metabolism. For this purpose, miRNAs were retrieved from miRBase database. After, Clustal Omega analyses were performed for alignment, and a phylogenetic tree was constructed via MEGA 11. Phylogenetic tree indicated that 14 miRNA sequences were clustered into four groups. One group consisted of mmu-miR-678, and the other 13 sequences were separated into three groups, revealing a close relationship among miRNAs. Findings from different studies provide a new perspective for potential miRNA-based biomarkers to detect lipid metabolism disorders, cardiovascular diseases as well as related disorders.

1. Introduction

miRNAs are a class of non-coding RNAs (ncRNAs) with a length of 20-22 nucleotides [1]. These short ncRNAs have an important role in the regulation of gene expression [2]. The human gene encodes more than 2300 miRNAs [3]. miRNAs are formed from their distinctive hairpin structure by RNA polymerase II. Processing of pri-miRNA and pre-miRNA in the nucleus yields mature double-stranded miRNA. The binding of mature miRNA and its complementary sequences with mRNA acts as a post-transcriptional repression, degradation, and silencing mechanism [2]. These tasks include vital events such as cell survival, growth, proliferation and disease resistance controlling tumor formation [2,4,5].

In addition, many studies are reporting the relationships among miRNAs and nutrigenomics [6-8]. Nutrigenomics examines the effect of nutrients on gene expression while nutrigenetics is related to the phenotypic responses of nutrients in the body [9]. Nutrigenomics plays an important role in identifying genes that cause diet-related diseases, revealing the mechanisms underlying these differences and determining a personalised diet approach [10]. Nutrigenomics examines food-gene interaction in three areas. First, it can act as a transcription factor that can bind to DNA as a result of the interaction of nutrients with receptors and change gene expression. Secondly, consumed foods can cause epigenetic changes. Finally, responses to diet may vary due to genetic differences among individuals [11].

Nutrigenomics provides valuable information to identify and integrate the relationships between foods or food-based metabolites and gene expression on a genome-wide level [12]. One of the important goals of nutrigenomic research is to control systemic chronic inflammation that adversely affects human health. Since systemic chronic inflammation may increase the risk of developing diseases such as metabolic syndrome, cardiovascular diseases, neurodegeneration and cancer, the effects of genes can be modified by foods or bioactive components in foods. High-throughput omics technologies help to reveal the relationships between diet and disease by examining the interaction of bioactive nutrient components with the genome at the cellular and molecular levels [10].

In this study, we aimed to investigate the evolutionary relationships of different miRNAs associated with cardiovascular diseases and lipid metabolism which are characterised as important diseases in nutrigenomics. For this purpose, alignment analysis was performed using Clustal Omega and a phylogenetic tree was constructed via MEGA 11.

2. Material and Method

In literature, there are several studies mentioned disease-related miRNAs and also their targets. Among them, we restricted our investigations for lipid metabolism and also cardiovascular diseases. For this purpose, miRNAs related to them were determined and then these miRNAs' sequences were retrieved from miRBase. Table 1 showed miRNAs used in this study and their target genes in relevant diseases.

Obtaining miRNAs were used for alignment analyses by using Clustal Omega (https://www.ebi.ac.uk/Tools/msa/clustalo). After, a phylogenetic tree was constructed via MEGA 11 with adjusted parameters including the neighbour-joining (NJ) method, genetic distances computed using p-distance model and even bootstrap resampling using 10.000 replicates [23-26].

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Table 1. miRNAs and target genes in diseases

miRNA	Target Gene	Relevant Region/Disease	References
miR-149	*AKT1* *E2F1*	*AKT1* encodes one of three members of the human AKT serine-threonine protein kinase family, designated as alpha, beta, and gamma. *E2F1* is a member of the E2F family of transcription factors, playing a very important role in the control of the cell cycle and the effect of tumour suppressor proteins.	Lin et al. [13]
miR-374	*C/EBP-β*	*C/EBP-β* modulates the expression of genes involved in cell cycle regulation and body weight homeostasis. Mutation of this gene is associated with acute myeloid leukaemia.	Pan et al. [14]
miR-678	*AGT*	The protein encoded by this gene is expressed in the liver and degraded by the enzyme renin in response to low blood pressure. Protein plays a role in the maintenance of blood pressure, body fluid and electrolyte homeostasis and the pathogenesis of essential hypertension and preeclampsia. Mutations in this gene are associated with susceptibility to essential hypertension and can cause renal tubular dysgenesis, a severe renal tubular developmental disorder.	Goyal et al. [15] Banik et al. [16]
miR-201			
miR-698			
miR-27			
miR-199	*mTOR*	It belongs to a family of phosphatidylinositol kinase-related kinases. It mediates cellular responses to stresses such as DNA damage and nutrient deprivation. It is a component of two separate complexes, mTORC1, which controls protein synthesis, cell growth and proliferation, and mTORC2, which is a regulator of the actin cytoskeleton and promotes cell survival and cell cycle progression. This protein serves as the target for cell cycle arrest and immunosuppressive effects of the FKBP12-rapamycin complex. mTOR inhibitors are used as immunosuppressants in organ transplants.	Alejandro et al. [17]
miR-342			
miR-122	*PPARα* *CPT1α*	*PPARα* regulates the expression of genes involved in fatty acid beta-oxidation and is an important regulator of energy homeostasis.	Gatfield et al. [18] Wei et al. [19]
miR-429	*ACE-2*	*ACE-2* is the primary enzyme in the renin-angiotensin system. It could play a critical gene in chronic kidney disease. Moreover, *ACE2* inhibits epithelial-mesenchymal transition via regulating vimentin and α-SMA.	Zhang et al. [20]
miR-370	*CPT1α*	*CPT1α* is a key enzyme in carnitine-dependent transport across the mitochondrial inner membrane, and its deficiency results in a reduced rate of fatty acid beta-oxidation.	Benatti et al. [21]
miR-130	*PPARγ*	*PPARγ* is a regulator of adipocyte differentiation. It has been implicated in the pathology of many diseases including obesity, diabetes, atherosclerosis, and cancer.	Pan et al. [14]
miR-330	*AGTR2*	It belongs to the G-protein coupled receptor 1 family and functions as a receptor for angiotensin II. It is an integral membrane protein that is highly expressed in the fetus and neonate, but slightly expressed in adult tissues except for the brain, adrenal medulla, and atretic ovary.	Sebastiani et al. [22]
miR-770			

***PPARα,** Peroxisome proliferator-activated receptor alpha; ***CPT1α,** Carnitine palmitoyltransferase I; ***PPARγ,** Peroxisome proliferator-activated receptor gamma, ***C/EBP-β,** CCAT enhancer binding protein beta; ***TNFRSF4,** Tumor necrosis factor receptor superfamily member 4; ***FST,** Follistatin; ***TNFα,** Tumour necrosis factor alpha; ***IL-6,** Interleukin 6; ***TLR4,** Toll-like receptor 4; ***IRS-1,** Insulin receptor substrat 1; ***mTOR,** mammalian target of rapamycin; ***ACE-1.2,** Angiotensin converting enzyme; ***AT-2,** Anjiyotensin II type-2

3. Result

miRNA sequences belonging to *Homo sapiens* and *Mus musculus* related to lipid metabolism and cardiovascular disease were retrieved from miRBase. Alignment analysis indicated similarities among sequences (Figure 1).

A phylogenetic tree was constructed by analysing 14 miRNAs. Sequences were clustered into four separate groups. mmu-miR-678 is found in one distinct clade. The second group consisted of three miRNAs including hsa-miR-199a-3p and hsa-miR-122-3p. Moreover, mmu-miR-201-5p belonged to single clades which were basal to the branch containing other miRNAs. hsa-miR-770-5p and hsa-miR-374c-5p were found in single clades but other miRNAs indicated homology among them in the third group. hsa-miR-130a-5p was a sister group to hsa-miR-330-3p whereas hsa-miR-149-3p showed homology to hsa-miR-27a-5p in this group. The remaining four miRNAs which are hsa-miR-370-3p, hsa-miR-429, mmu-miR-698-5p and hsa-miR-342-3p formed the fourth group (Figure 2).

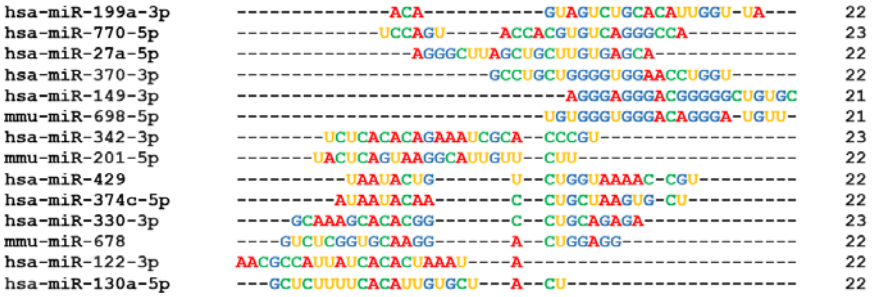

Fig. 1. Clustal Omega results of miRNAs

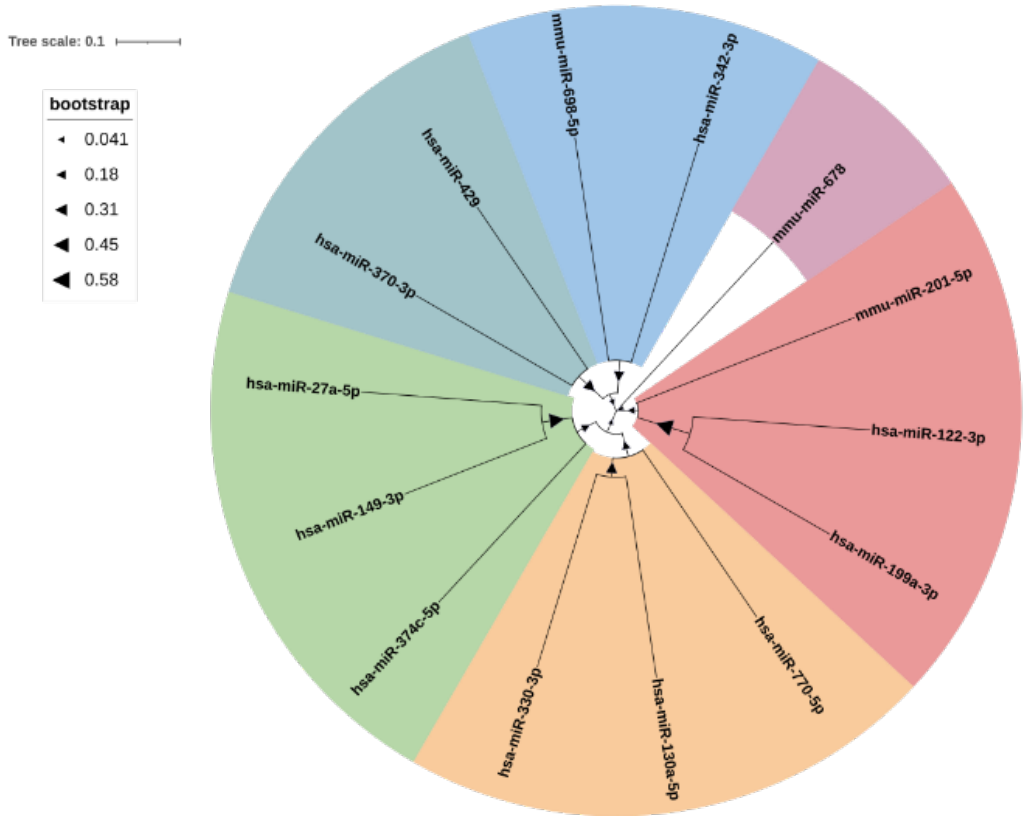

Fig. 2. Phylogenetic tree

4. Discussion

It is important to regulate dietary programs to prevent diseases. Nowadays, cardiovascular diseases have commonly observed both in females and males all over the World. Therefore, nutrigenomic studies have gained attention to identify relationships between nutrition and gene expression. For this purpose, we determined the relationships among miRNAs which are involved in similar metabolic pathways. 14 different miRNAs belonging to human and mouse including hsa-miR27a-5p, hsa-miR149-3p, hsa-miR374c-5p, mmu-miR-678, mmu-miR-698-5p, hsa-miR-199a-3p, hsa-miR122-3p, hsa-miR342-3p, mmu-miR201-5p, hsa-miR429, hsa-miR370-3p, hsa-miR130a-5p, hsa-miR330-3p and hsa-miR770-5p showed similarities and evolutionary relationships.

There are many different studies to identify miRNA and disease relationships [27-29]. miR678 analysed in this study is one of them. The first group in the tree consisted of only mmu-miR-678 sequences. There are limited investigations related miR678 and diet. These studies reported that lipid metabolism and also metabolic pathways in obesity are regulated by miR678 [15, 30, 31].

We determined that hsa-miR-199a-3p, hsa-miR122-3p and mmu-miR201-5p were found in the second group in tree. Yeligar et al. [32] observed an increase in the mRNA expression of endothelin-1, hypoxia-inducible factor-1α, and inflammatory cytokines in sinusoidal endothelial cells in ethanol-fed rats compared to the control group. They also reported that miR-199 reduced the expression of hypoxia-inducible factor-1α and endothelin-1. In addition, increased expression of miR-199-3p and miR-342 was observed in tissue pieces taken from offspring of mothers fed a low protein diet. Moreover, it was observed that mTOR and insulin secretion were normalised as a result of blocking the expression of these miRNAs [17]. Paula et al. [33] also investigated miRNA expression in slow and fast muscles of

Piaractus mesopotamicus both when nutrient-restricted and refeeding. Experimental data showed that miR-199 and other miRNAs were up-regulated during refeeding and reduced expression of target genes.

Another miRNA which is investigated in this study is miR-122. miR-122 is a key regulator of cholesterol and fatty acid metabolism in the adult liver [34]. In cultured HepG2 cells, it was indicated that miR-122 and miR-370 play a role in the accumulation of hepatic triglycerides by miR-122 and miR-370 effects [35]. Similarly, Gao et al. [36] reported the increase in miR-122 levels in patients with hyperlipidaemia. Moreover, Baselga-Escudero et al. [37] examined whether miR-122 levels in rat liver are associated with lipidemia in nutritional models. The research has shed new light on the regulation of miR-122 in a dyslipidemic model of obese rats and how these miRNAs are modulated by dietary components in the liver and peripheral blood mononuclear cells (PBMCs). In this respect, maternal diet is an important parameter to identify the effects of this diet on baby. For this purpose, Benatti et al. [21] evaluated the modulation of hepatic fatty acid synthesis, β-oxidation pathways, miR-122 and miR370 expression in recently weaned baby mice (day 28) fed a maternal diet. According to experimental data, it was observed that a maternal high-fat diet affected early lipid metabolism by modulating the expression of β-oxidation-related genes, miR-122 and miR-370, which may cause metabolic problems in adult life. de Paula Simino et al. [38] also analysed the same miRNAs and suggested that a maternal high-fat diet applied during pregnancy and lactation causes permanent changes in the lipid metabolism of the offspring. Furthermore, López et al. [39] determined the relationships between inflammation and iron homeostasis with obesity causing epigenetic changes over generations via gametes. As a result of the research, it was observed that the expression of miR-122, which is associated with inflammation and iron metabolism, increased in the systemic and sperm levels of obese subjects. There are several studies to examine miR122 and obesity associations [40-42].

miR27 is another miRNA sequence related to lipid

metabolism. Qin et al. [43] reported that 3-O-[(E)-4-(4-cyanophenyl)-2-oxobut-3-en-1-yl] kaempferol (Fla-CN) treatment ameliorated metabolic lipid disorders and increased miR-27 expression. Another investigation was carried out by Goyal et al. [15]. They analysed whether a maternal low-protein diet administered in the prenatal period causes epigenetic changes in the gene expression of the brain renin-angiotensin system in mouse fetus. They recorded significant changes in mRNA and protein expression in the fetal brain renin-angiotensin system, and even upregulation of miR-27a and miR-27b but downregulation of miR-330, which are the main regulators of hypertension in adults. In addition to this system, it was concluded the expression levels of miR-27 associated with obesity in adipose tissues from different groups [44]. Similar results were suggested by Zou et al. [45], investigating the effects and mechanisms of persimmon tannin on adipogenic differentiation. As a result of the experiment, persimmon tannin caused adipocyte differentiation via PPARγ and miR-27. On the other hand, Sardu et al. [46] evaluated inflammation/oxidative stress, miRNA expression, and cardiovascular function at 12-month follow-up in prediabetes patients treated with metformin. They reported that metformin reduces inflammation/oxidative stress and even miR-27 expression in obese prediabetes.

miR27 and miR149 indicated homology as a result of phylogenetic analysis in our study. Similar to miR27, miR149 is related to lipid and carbohydrate metabolisms. Increased level of miRNA showed enhanced long-chain fatty acids and suppressed the increase in glucose-induced damage and even reduced vascular damage [47, 48]. Shibayama et al. [49] observed changes in the expression of hepatic miRNA and genes related to lipid metabolism after 60 weeks of a high-fat diet administered to mice. It was reported that experimental data up-regulation of miR-149-3p was beneficial against tumours originating from a high-fat diet. In bovine, Khan et al. [50] reported that bta-mir-149-5p could negatively control adipocyte proliferation and differentiation. In addition, miR149 can be a marker for anti-inflammatory effects [51]. Chen et al. [52] identified whether non-alcoholic fatty liver disease can cause inflammation and apoptosis through endoplasmic reticulum stress. They also reported that up-regulation of miR-149 reduced apoptosis and inflammation caused by endoplasmic reticulum stress.

In phylogenetic tree, hsa-miR374 was found in the same group of hsa-miR27 and hsa-miR149. Similar to them, miR374 is related to diabetes. Paramasivam et al. [53] found the changes in expression of miR-128-3p, miR-374a-5p, miR-221-3p and miR-133a-3p to prevent the development of diabetes. hsa-miR374 together with let-7d could also be useful for the risk of birth with a small fetus for gestational age [54]. In addition, Tan et al. [55] identified 53 potential miRNAs (miR-21-3p, miR-374a-5p, 144-3p, miR-500a-3p, etc.) for celiac disease.

hsa-miR130a-5p showed sequence homology with hsa-miR330-3p and hsa-miR770-5p. Kim et al. [56] revealed a direct correlation miR-130 levels in white adipose tissues from adipocytes stimulated with TNFα and mice on a high-fat diet. Pan et al. [57] also reported that miR-130 was able to reduce epididymal fat accumulation and partially regulate glucose tolerance in a good way by suppressing PPAR-γ in obese mice. To support this, Zhang et al. [58] fed mice a high-fat diet to analyse the polarisation of miR-130b to cause type 2 diabetes in mice. As a result, it has been reported that miR-130b is a regulator of macrophage polarisation and beneficial against adipose tissue inflammation. In another study, Al-Rawaf [59] investigated miRNA profile according to the degree of obesity in adolescents. Circulating miRNAs including miR-130, showed significant correlation with plasma levels of adipokines.

miR-330 has been also analysed in several studies. Yang et al. [60] measured miRNA expression in the livers of mice fed a high-fat diet with Affymetrix GeneChip miRNAs. They reported changes in several miRNA levels, including miR-330. Sun et al. [61] controlled the level of miR-330-5p by feeding 8-week-old mice with a high-fat diet for 8 weeks. As a result, it has been reported that a high-fat diet increases miR-330-5p levels which causes insulin tolerance in diabetic mice. On the other hand, Ortega et al. [62] investigated whether a diet enriched with nuts alters miRNA expression through long-chain polyunsaturated fatty acids. They revealed a decrease in miR-330-3p expression and changes in many miRNA levels. In addition to lipid metabolism, there are also relationships between glucose and miR330. Sebastiani et al. [22] reported an inverse correlation between miR-330-3p level and insulinemia in their miRNA analysis in patients with gestational diabetes mellitus. Similarly, Pfeiffer et al. [63] analysed miRNAs from circulating miRNAs associated with insulin secretion defects and glucose homeostasis in patients with gestational diabetes mellitus and non-patient control groups. As a result of the study, upregulation of miR-330-3p expression was reported in gestational diabetes mellitus patients compared to the control group.

Increased the expression of miR-770-3p was also reported by Lee et al. [64]. They investigated the expression change on exosomal miRNAs found in the serum of aged mice after a short-term calorie-restricted diet. As a result of the experiment, it was observed that the expression of miR-770-3p and miR-500-3p increased in direct proportion with aging, but calorie-restricted diet decreased the expression of miR-770-3p and miR-500-3p. In addition, experimental data have shown that miR-770-5p is an important regulator of pancreatic β-cell proliferation, apoptosis and insulin secretion and that miR-770-5p dysregulation leads to the development of gestational diabetes mellitus [65]. Min Wang et al. [66] observed that miR-770-5p was significantly increased in the serum of patients with type 2 diabetes mellitus, as a result of reverse transcription-quantitative PCR.

In the fourth group, hsa-miR342-3p was found in the sister clade of mmu-miR-698-5p whereas hsa-miR-429 indicated homology to hsa-miR370-3p. hsa-miR342-3p, and mmu-miR-698-5p showed similarities although they belong to different species. Chartoumpekis et al. [67] examined the possible effects of miRNA during obesity formation in mice fed with a high-fat diet. As a result of the research, up-regulation of mmu-miR-222, mmu-miR-342-3p, mmu-miR-142-3p, mmu-miR-124-5p, mmu-miR-21, mmu-miR-146a, and down-regulation of mmu-miR-200b, mmu-miR-200c, mmu-miR-204, mmu-miR-193, mmu-miR-378, mmu-miR-146b, mmu-miR-379, mmu-miR-122, mmu-miR-133b, mmu-miR-1, mmu-miR-30a, mmu-miR-192 were reported. To support this, up-regulation of miR-342-3p was observed in the brain and adipose tissues of mice fed a high-fat and high-sucrose diet [68]. Matboli et al. [69] also analysed this miRNA in a different aspect. They evaluated the anti-diabetic nephropathy effect of caffeic acid by suppressing autophagy-regulating miRNAs in mice. As a result of the experiment, it was revealed that caffeic acid can be used against diabetic kidney disease by suppressing miR-342, miR-133b and miR-30a. Homology to hsa-miR342-3p, mmu-miR-698-5p was investigated in germline epigenome. For this purpose, Galan et al. [70] mentioned an overview of paternity effect paradigms. They reviewed how epigenetic changes in sperm cause physiological changes in the offspring's later life and the effect of miR-698 on this phenomenon.

hsa-miR429 showed an evolutionary relationship with hsa-miR370-3p. Sene et al. [71] studied podocyte simplification and deletion of the foot process in mice on a low-protein diet. Low protein glomeruli isolated in the experiment showed low levels of miR-200a, miR-141 and miR-429. In another study, Peng et al. [72] revealed the role of miR-429 in subcutaneous and intramuscular preadipocyte proliferation and differentiation in

pigs. Chao et al. [73] also examined the mechanism of abdominal fat accumulation in chickens. As a result of miRNA sequencing, it was observed that miR-429-3p was highly expressed in a high fat chickens. Furthermore, Nguyen et al. [74] examined the role of miR-429-3p on myoblast proliferation and myogenic differentiation in their experiment.

On the other hand, Gao et al. [36] investigated the relationship of circulating lipometabolism-related miRNAs with the presence of coronary artery disease in hyperlipidaemia patients in their experiment. As a result of the experiment, they found that increased miR-370 levels in plasma could provide information about coronary artery disease in hyperlipidaemia patients. Zhang et al. [75] determined how salidroside regulates lipid metabolism via miR-370 both in-vitro and in-vivo. They suggested that salidroside can regulate lipid metabolism in the liver by down-regulating miR-370 expression in type-2 diabetes mice. Furthermore, Chu et al. [76] analysed the roles of miR-370 on lipid accumulation in their experiment, revealing miR-370 is a good regulatory target to reduce back fat in pigs and fight obesity in humans. Concordant with their results, hepatic miR-370-122-let7 can be used to determine the first step in the early stages of non-alcoholic fatty liver disease [77].

5. Conclusion

Nutrigenetics, nutrigenomics and epigenetic mechanisms are efficient and precise areas in defining changes in gene expression. In this respect, miRNAs have been widely analysed as biomarkers in different diseases. Therefore, it is important to determine evolutionary relationships among miRNAs which play important roles in different diseases. In this respect, there are several miRNAs have been widely used as biomarkers for cancer diagnosis. Even though miRNA-based diagnostics are still in their infancy, they have enormous potential for future illness diagnostics and even gene therapy. To our best knowledge, this is one of the first reports to analyse these miRNAs in nutrigenomics and epigenetics manner.

Declaration of conflicting interests

The authors declare no competing interests.

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