HEPATOLOGY FORUM

doi: 10.14744/hf.2021.2021.0037

The relationship between polyphenols and miRNAs: A novel therapeutic strategy for metabolic associated fatty liver disease

Hatice Merve Bayram[1], Fatih Eren[2,3], Fatma Esra Gunes[4]

[1]Department of Nutrition and Dietetics, Istanbul Gelisim University Faculty of Health Sciences, Istanbul, Turkey; [2]Institute of Gastroenterology, Marmara University, Istanbul, Turkey; [3]Department of Medical Biology, Marmara University School of Medicine, Istanbul, Turkey; [4]Department of Nutrition and Dietetics, Marmara University Faculty of Health Sciences, Istanbul, Turkey

Abstract

Metabolic-associated fatty liver disease (MAFLD) is a public health problem that is increasingly recognized, currently affecting up to a quarter of the world's adult population. Although a biopsy is the current gold standard to diagnose MAFLD, there are potentially serious complications, making it inadequate. Thus far, noninvasive methods have not been able to determine the stage and the subtype of MAFLD. The development and prognosis of MAFLD are modulated by epigenetic factors, including microRNAs (miRNAs), which may be potential biomarkers for MAFLD. Polyphenols, found in many fruits and vegetables, may be useful, as they alter gene expression with epigenetic factors, such as miRNAs. This review presents an overview of the relationship between polyphenols and miRNAs in MAFLD. The literature suggests that miRNAs could be used as a diagnostic method for MAFLD, especially miRNA-122 and miRNA-34a. However, though it has been demonstrated that polyphenols may contribute to improving MAFLD, to our knowledge, no study to date has shown the relationship between polyphenols and miRNAs in MAFLD. The exact mechanisms of polyphenols on miRNAs in MAFLD remain unclear. Future studies may provide hope for diet therapy for MAFLD patients as well as the development of polyphenol-related foods or drugs that target miRNAs to treat MAFLD.

Keywords: Metabolic-associated fatty liver disease; microRNA; polyphenols.

Introduction

Metabolic (dysfunction)-associated fatty liver disease (MAFLD), previously known as non-alcoholic fatty liver disease (NAFLD), is the most common chronic liver disorder worldwide, thought to affect more than one-third of the general population (estimated to be 30% of adults in industrialized countries).[1,2] The high prevalence of MAFLD has been associated with increasing levels of an unhealthy diet and low physical activity seen worldwide.[3]

How to cite this article: Bayram HM, Eren F, Gunes FE. The relationship between polyphenols and miRNAs: A novel therapeutic strategy for metabolic associated fatty liver disease. Hepatology Forum 2021; 2(3):128–136.

Received: September 04, 2021; **Accepted:** September 10, 2021; **Available online:** September 15, 2021

Corresponding author: Fatih Eren; Marmara Universitesi, Gastroenteroloji Enstitusu, Istanbul, Turkey
Phone: +90 216 777 58 68; **e-mail:** fatiheren@marmara.edu.tr

MAFLD is a multisystem disorder with a complex pathophysiology.[1] It is recognized as the liver disease component of metabolic syndrome, and is associated with insulin resistance and genetic susceptibility. As the epidemic rates of obesity, type II diabetes mellitus, insulin resistance, and dyslipidemia continue to increase, the risk of MAFLD increases proportionately.[2,4]

In recent years, it has been demonstrated that epigenetic factors may cause the development of a wide range of diseases, including MAFLD, and miRNAs appear to have an important role.[5] Therefore, miRNAs have the potential for use in various clinical settings, such as early diagnosis and the monitoring of progression and response to treatment in various diseases.[6] Almost all genetic pathways, including transcription factors, secreted factors, receptors, and transporters, can be modulated by miRNAs.[7] Also, environmental conditions, such as stress and nutritional status, can modulate epigenetic factors, and so miRNAs may also be useful to assess the effects of diet and other lifestyle interventions.[8]

The value of polyphenols in functional foods is evident due to biological activity that includes antioxidant, anti-inflammatory, and anticancer behavior; regulation of lipid, carbohydrate, and amino acid metabolism; inhibition of platelet aggregation; and improvement of endothelial function.[9,10] Regular consumption of polyphenols has been associated with a reduction in the risk of several metabolic diseases, such as obesity, insulin resistance, hypertension, and cardiovascular disease.[11-13] Polyphenols may alter gene expression via epigenetic factors, such as miRNAs, by contributing to the modulation of key proteins.[14,15] Thus, they may contribute to the amelioration of MAFLD and other diseases, but the knowledge of the potential mechanisms of polyphenols and miRNAs in MAFLD remains limited. This review presents an overview of the known relationship between polyphenols and miRNAs in MAFLD.

Materials and Methods

A comprehensive electronic search of the Scopus, ScienceDirect, and PubMed databases was conducted to identify relevant studies. The keywords used were "phenolic" OR "polyphenol" AND "non-alcoholic fatty liver disease" OR "metabolic dysfunction-associated fatty liver disease" AND "miRNA" OR "microRNAs". Theses, editorials, letters to editor, and conference abstracts were excluded. The inclusion criteria were *in vitro*, *in vivo*, or human clinical studies of the effects of polyphenols on MAFLD-associated miRNAs. We did not find any human clinical studies. A total of 85 studies were included in this review.

The Role and Expression Level of miRNAs in MAFLD

miRNAs are endogenous, small non-coding RNAs that play a central role in regulating both mRNAs and the protein expression of target genes.[16] miRNAs are specific regulators that affect the stability or translation of the targeted mRNA. miRNAs are abundant in the liver and modulate a spectrum of cellular processes related to inflammation, proliferation, differentiation, cellular growth, tissue remodeling.[17,18] Therefore, since miRNAs can be detected in tissue and serum in a stable form, they are potential biomarkers for many liver diseases.[19]

Thousands of miRNAs have been identified, though their exact mechanisms remain unknown. Several miRNAs have shown anomalous expression in MAFLD (Fig. 1). One study identified 44 miRNAs with differential expression in MAFLD patients.[20] It has been reported that the serum level of miRNA-122, miRNA-34a, and miRNA-16 were upregulated in MAFLD patients compared with control groups, and that the level of miRNA-122 and miRNA-34a was correlated with the severity of MAFLD.[21] It was observed in another study that the serum level of miRNA-21, miRNA-34a, miRNA-122, and miRNA-451 were upregulated in MAFLD patients and that the serum level of miRNA-122 was positively associated with steatosis severity.[22] It has also been reported that hsa-miRNA-122-5p, hsa-miRNA-1290, hsa-miRNA-27b-3p, and hsa-miRNA-192-5p levels were higher in MAFLD patients and that miRNA levels were a more specific biomarker for MAFLD than alanine transaminase and fibrosis-4 index values.[23] An investigation of the serum level of miRNA-197, miRNA-146b, miRNA-10b, miRNA-181d, miRNA-34a, miRNA-122, miRNA-99a, and miRNA-29a in MAFLD patients yielded results indicating that the level of miRNA-181d, miRNA-99a, miRNA-197, and miRNA-146b were downregulated in MAFLD patients. Additionally, miRNA-197 and miRNA-10b were associated with the severity of inflammation while miRNA-181d and miRNA-99a levels were related to the serum level of gamma-glutamyltransferase in non-alcoholic steatohepatitis (NASH) patients.[24] It has also been noted that the serum level of miRNA-122 in mild steatosis patients was lower than that of severe steatosis patients, while the serum level of miRNA-122 in mild fibrosis patients was higher compared with that of severe fibrosis patients.[25] A study that analyzed 84 miRNAs in MAFLD patients showed that the serum level of miRNA-122, miRNA-192, miRNA-375, and miRNA-122 were upregulated in steatosis patients, and the serum level of miRNA-122 and miRNA-192 were significantly downregulated in NASH patients compared with the level observed in controls.[6] It was confirmed that the serum level of miRNA-21 was lower in NASH patients and that the serum level of miRNA-122 and miRNA-192 was differentially regulated in bland steatosis (NAFL) and NASH patients.[26] Similarly, the serum level of miRNA-21 was found to be lower in MAFLD patients.[27] It has been observed that the level of miRNA-122, miRNA-192, and miRNA-34a was associated with steatosis and inflammatory activity, and that only the miRNA-16 level was significantly correlated with fibrosis. It has also been reported that the serum level of miRNA-34a was lower in NASH patients than in MAFLD patients.[28] Furthermore, it was indicated that the serum level of miRNA-122 and miRNA-34a was higher, while the miRNA-331-3p and miRNA-30c levels were lower in MAFLD patients.[29] Another study found that the serum level of miRNA-122 and miRNA-34a was upregulated in MAFLD patients and strongly related with very-low-density lipoprotein and triglyceride (TG) levels.[30] The findings of other research confirmed that the serum level of miRNA-122 was upregulated in MAFLD patients.[31] It has also been reported that the expression of miRNA-122 was reduced in a morbidly obese group compared with moderately obese patients and that the miRNA-122 level was greater in morbid obese patients with NASH than in morbid obese patients with simple steatosis. The expression of miRNA-33b was greater in the NASH patients.[32] The findings of another study revealed that the serum level of miRNA-301 and miRNA-34a-5p were upregulated and miRNA-375 was downregulated in MAFLD patients. In addition, increased expression of miRNA-301a and miRNA-375 was noted in hepatocellular carcinoma patients.[33] Other researchers found that 14 miRNAs were associated with MAFLD and that the liver levels of miRNA-139-5p, miRNA-30b-5p, miRNA-122-5p, and miRNA-422a were lower and the level of miRNA-146b-5p was higher in obese patients with MAFLD compared with a control group.[34] It has also been demonstrated that miRNA-22,miRNA-29a, and miRNA-663a were upregulated in MAFLD patients.[35] Similarly, another study noted that miRNA-34a, miRNA-192, miRNA-27b, miRNA-122, miRNA-22, miRNA-21, miRNA-197, miRNA-30c, and miRNA-16 were correlated with MAFLD severity.[36] Table 1 provides details of studies about miRNA levels and Table 2 summarizes some possible miRNA pathways in MAFLD patients.

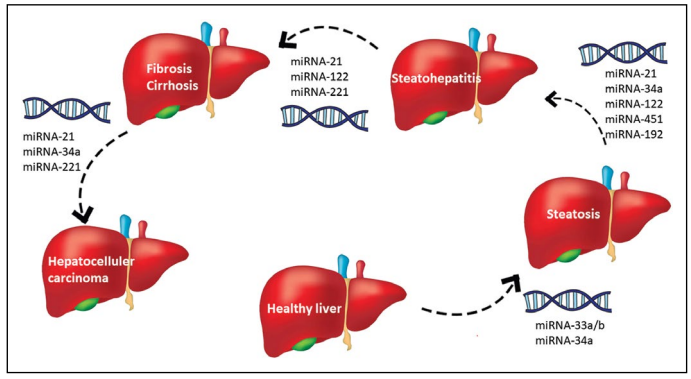

Figure 1. The role of miRNAs in key transitions of the pathogenesis of non-alcoholic fatty liver disease.

MiRNA: MicroRNA.

The Relationship between Polyphenols and miRNAs

Polyphenols are secondary metabolites that are abundant in fruits and vegetables as well as other products, including coffee, tea, red wine, and dark chocolate.[14,37,38] Polyphenols are classified into 2 main groups: flavonoids and non-flavonoids. The non-flavonoids include subgroups of phenolic acids, stilbenes, and lignans. The main subgroups of flavonoids are flavanols, flavan-3-ols, isoflavones, and anthocyanidins, and minor flavonoid subgroups include flavan-3,4-diols, dihydroflavonols, chalcones, dihydrochalcones, coumarins, and aurones.[37] A dietary intake of polyphenols was estimated at 1-1.2 g per day, 40% of which were flavonoids.[9] Only 5% to 10% of polyphenols ingested are absorbed in the small intestine. During the process of absorption, polyphenols are often conjugated in the small intestine and later in the liver. The non-absorbable portion passes to the colon and is metabolized by intestinal microbiota.[14]

Polyphenols have been shown to have various therapeutic properties, such as antioxidant, anti-inflammatory, antidiabetic, antiallergic, antimicrobial, and anticancer effects, as well as improved lipid metabolism.[39] Most of the therapeutic effects of polyphenols have been linked to altering gene expression that encodes essential metabolic

Table 1. miRNA analysis in MAFLD patients

Study group	Biopsy	Method	Upregulated miRNAs	Downregulated miRNAs	References
Control group (n=19), MAFLD (n=34)	Yes	qRT-PCR	122, 34a (NASH), 16 (MAFLD)		Cermelli et al., 2011[21]
Control group (n=311), MAFLD (n=92)	No	RT-PCR	21, 34a, 122, 451 (MAFLD)		Yamada et al., 2013[22]
Control group (n=90+(80)), MAFLD (152+(103))	Yes	qRT-PCR	hsa-miRNA-122-5p, hsa-miRNA-1290, hsa-miRNA-27b-3p,hsa-miRNA-192-5p (MAFLD)		Tan et al., 2014[23]
Control group (n=20), MAFLD (n=20)	Yes	qRT-PCR		181d,99a,197,146b (MAFLD)	Celikbilek et al., 2014[24]
MAFLD (n=52)	Yes	TaqMan Micro-RNA assays	122 (steatosis)	122 (fib.)	Miyaaki et al., 2014[25]
Control group (16+(19)), MAFLD (16+(30)), NASH (16+(47))	Yes	RT-PCR	122,192,375 (NASH),122 (Fib)		Pirola et al., 2015[6]
Control group (n=61), MAFLD (n=50), NASH (n=87)	Yes	qRT-PCR	122,192,21 (NASH)		Becker et al., 2015[26]
Control group (n=12), MAFLD (n=25)	No	qRT-PCR		21 (MAFLD)	Sun et al., 2015[27]
Control group (n=37), MAFLD (n=17), NASH (n=31)	Yes	qRT-PCR	122,192,34a (NASH), 16,21,146 (MAFLD)		Liu et al., 2016[28]
Control group (n=62), NALFD (n=18)	No	RT-PCR	122,34a (MAFLD)	331-3p,30c (MAFLD)	Zarrinpar et al., 2016[29]
Control group (n=28), MAFLD (n=36)	Yes	qRT-PCR	122,34a (MAFLD)		Salvoza et al., 2016[30]
MAFLD (n=305)	Yes	TaqMan Micro-RNA assays	122 (steatosis, inf., ballooning and fib.)		Akuta et al., 2016[31]
Control group (n=31), MAFLD (n=27), NASH (n= 34)	Yes	RT-PCR	122 (NASH)		Auguet et al., 2016[32]
Control group (n=10), MAFLD (n=12), NASH (n=11), cirrhosis (n=3)	Yes	RT-PCR	miR-301a-3p and miR-34a-5p	375	Guo et al., 2016[33]
Control group (n=19), borderline (n=24), MAFLD (17),	No	RT-PCR	146-5p	139-5p, 30b-5p, 122-5p, 422a	Latorre et al., 2017[34]
Control group (n=10), MAFLD (n=44)	Yes	RT-PCR	22,29a (NASH), 663a (MAFLD)		López-Riera et al., 2017[35]
Control group (n=17), MAFLD (n=46), NASH (n=50), fibrosis (n=29)	Yes	RT-PCR	34a-5p,27b-3p,22-3p,122-5p, 192-5p (MAFLD and NASH) 27b-39, 21-5p,122 (fib.)	30c-5p, 16-5p, 197-3p (MAFLD) 16-5p, 30c-5p (NASH and fib.)	López-Riera et al., 2018[36]

MAFLD: Metabolic-associated fatty liver disease; MiRNA: Micro RNA; NASH: Non-alcoholic steatohepatitis; PCR: Polymerase chain reaction; qRT-PCR: Quantitative real-time PCR; RT-PCR: Real-time PCR.

Table 2. Possible microRNA pathways in metabolic-associated fatty liver disease

miRNA	Pathway
miRNA-122[61-64]	Lipid metabolism (cholesterol, VLDL, TG, HMGCR), carcinogenesis
miRNA -10b[65]	Lipid metabolism (PPAR-α)
miRNA -33[66-68]	ABCA1 transport, ABCG1, Niemann Pick (NP) -C1, insulin signal pathway
miRNA -34[6,21,61,69-71]	AMPK phosphorylation, miR-34a/SIRT1/p53 activation, MAFLD progression, lipid metabolism
miRNA -192[72,73]	MAFLD progression
miRNA -214-5p[74]	MAFLD progression
miRNA -27a/b[75]	Lipid metabolism
miRNA -24[76]	Lipid metabolism (Insig1)
miRNA -451[77]	Inflammation
miRNA -1290, miRNA -27b-3p[78]	Variable
miRNA -192-5p[79]	Lipid metabolism (SCD-1)
miRNA -103/107[8,80,81]	PANK1-3, lipid metabolism, development of insulin resistance, PPAR-α, caveolin-1
miRNA -155[82,83]	Inflammation and liver injury, SREBP-lc, LXRα- lipid metabolism
miRNA -29[61]	SIRT1, HMGCR, LPL
miRNA -467b[84]	LDL metabolism
miRNA -143[85]	FABP4, SLC2A4, PPARγ, and LIPE

ABCA1: member 1 of human transporter sub-family ABCA; ABCG1: Adenosine 5'-triphosphate-binding cassette subfamily G member 1; AMPK: Adenosine monophosphate-activated protein kinase; FABP4: Fatty acid-binding protein 4; HDL: High-density lipoprotein; HMGCR: 3-hydroxy-3-methyl-glutarylcoenzyme A reductase; LDL: Low-density lipoprotein; LIPE: Hormone-sensitive lipase; LPL: Lipoprotein lipase; LXRα: Liver X receptor R-alpha; MAFLD: Metabolic-associated fatty liver disease; MiRNA: MicroRNA; NP-C1: Niemann Pick-C1; PANK1-3: Pantothenate kinase 1-3; PPAR-α: Peroxisome proliferator-activated receptor-alpha; PPARγ: Peroxisome proliferator-activated receptor γ; SCD-1: Stearoyl-CoA desaturase 1; SIRT-1: Sirtuin-1; SLC2A4: Solute carrier family 2, facilitated glucose transporter member 4; SREBP-lc: Sterol regulatory element-binding transcription factor 1; TG: Triglycerides; VLDL: Very-low-density lipoprotein.

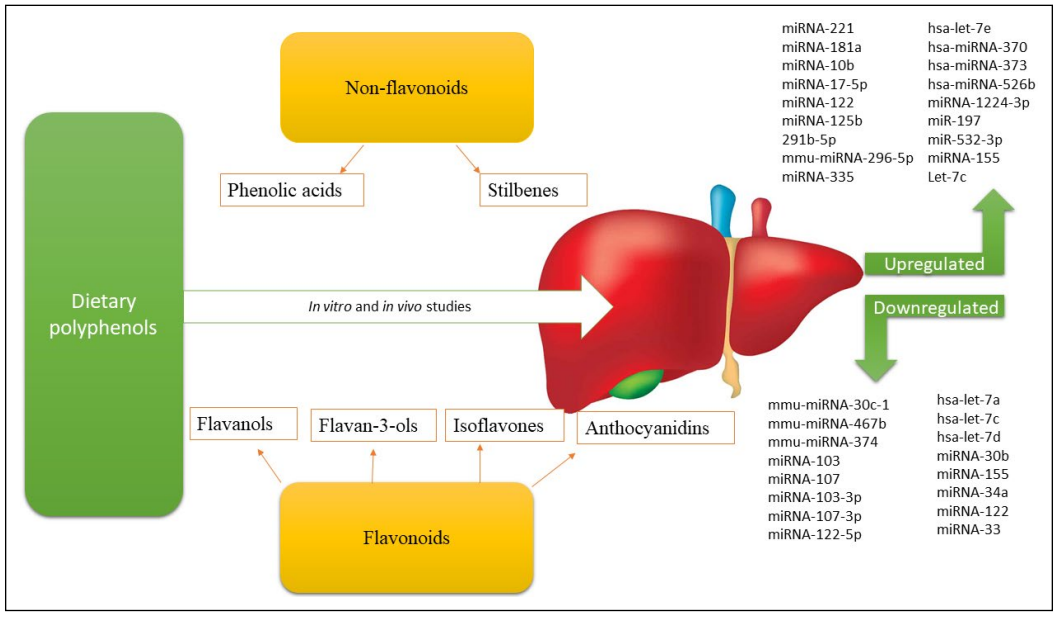

Figure 2. Possible effects of polyphenols on MAFLD-associated miRNAs.

MAFLD: Metabolic-associated fatty liver disease; MiRNA: MicroRNA.

proteins. These gene modifications may result from the interaction of polyphenols with epigenetic factors, such as signal cascades and/or miRNAs.[18] Modulation of miRNAs by polyphenols appears to be a potential new strategy to regulate metabolism and related diseases;[40] however, the precise mechanisms are not yet known.[9,14] In recent years, the beneficial effects of polyphenols in MAFLD patients have begun to attract attention and it has been demonstrated that the therapeutic effects of polyphenols may contribute to improvement of MAFLD.[41] Investigation of miRNA pathways continues.

Our review revealed no study evaluating the relationship between polyphenols and miRNAs in MAFLD. Therefore, we focused on the relationship between polyphenols and miRNAs that may have an impact on liver disease and diseases caused by MAFLD (Fig. 2).

Table 3. Summary of in vitro and in vivo studies

Model	Study design	Polyphenols	Method	Upregulated miRNAs	Downregulated miRNAs	References
In vitro	Human hepG2 cells, 3.125, 6.25, 12.5, 25 and 50 µg/ml, 72 h	Ellagitannins	qRT-PCR	hsa-let-7e, hsa-miRNA-370,hsa-miRNA-373 and hsa-miRNA-526b	hsa-let-7a, hsa-let-7c and hsa-let-7d	Wen et al., 2009[43]
In vitro	Human hepG2 cells, 50 mg/L of EGCG, 100 mg/L of GSPE or 100 mg/L of CPE, 5 h	GSPE, CPE or EGCG	qRT-PCR	miRNA-1224-3p, miR-197 and miR-532-3p (GSPE or CPE)	miRNA-30b (GSPE, CPE, EGCG)	Arola-Arnal et al., 2011[15]
In vitro	3T3-L1 maturing pre-adipocytes, 25 µM, 8 days	Resveratrol	RT-PCR	miRNA-155		Eseberri et al., 2017[45]
In vitro	Human pre-adipocytes, 25 µmol/L, 6 h	Extra-virgin olive oil polyphenols	qPCR	Let-7c	miRNA-155, miRNA-34a	Carpi et al., 2019[47]
In vitro In vitro	FAO cells, 25 mg/L for 5 h Male Wistar rats, 250 mg/kg, 3 h	GSP	qRT-PCR		miRNA-122, miRNA-33	Baselga-Escudero et al., 2012[42]
In vitro In vivo	Human hepG2 cells, 0.02, 0.2, 2 and 20 µg/mL, 24 h Male Sprague Dawley rats, 20mg/kg, 16 weeks	EGCG Green tea	qRT-PCR	miRNA-221, miRNA-181°, miRNA-10b		Arffra et al., 2016[44]
In vitro In vivo	3T3-L1 maturing pre-adipocytes, 25 µM, 24 h Male C57BL/6 mice, 2-10 µM, 7 days	Curcumin	RT-PCR	miRNA-17-5p		Tian et al., 2017[46]
In vivo	Male C57BL/6J mice, 0.5 to 1.0% CPP, 15 weeks	Coffee polyphenols	RT-PCR	miRNA-122		Murase et al., 2011[50]
In vivo	Female C57BL/6J mice, 0, 0.2 or 2 mg/g, 6 weeks	Quercetin	RT-PCR	miRNA-122 miRNA-125b		Boesch-Saadatmandi et al., 2012[49]
In vivo	C57B6/J mice or apoE2/2 mice, 0.006% of the diet, 8 weeks	Quercetin, hesperidin, naringenin, anthocyanin, catechin, curcumin, proanthocyanin, caffeic acid, and ferulic acid	qRT-PCR	291b-5p, mmu-miRNA-296-5p	mmu-miRNA-30c-1, mmu-miRNA-467b and mmu-miRNA-374	Milenkovic et al., 2012[52]
In vivo	Male mice deficient in LDL receptor in a C57BL/6J, high dose, 10 weeks	Quercetin	qRT-PCR		miRNA-103, miRNA-107, miRNA-122	Joven et al., 2012[51]
In vivo	Male Sprague-Dawley rats, 30 mg/kg, 6 weeks	Resveratrol	RT-PCR		miRNA-103-3p, miRNA-107-3p, miRNA-122-5p	Gracia et al., 2017[53]
In vivo	Mice, 500 mg/kg, 12 weeks	Green tea	qRT-PCR	miRNA-335		Otton et al., 2018[52]

CPE: Cocoa proanthocyanidin extract; EGCG: Pure epigallocatechin gallate isolated from green tea; FAO: A rat hepatoma cell line; GSP: Grape seed proanthocyanidin; GSPE: Grape seed proanthocyanidin extract; MiRNA: MicroRNA; PCR: Polymerase chain reaction; qPCR: Real-time quantitative polymerase chain reaction; qRT-PCR: Quantitative real-time PCR; RT-PCR: Real-time PCR.

i. *In Vitro* Studies

Polyphenols have been shown to improve lipid metabolism, inhibit adipogenesis and inflammation, and also provide antioxidant effects in cell line studies. Therefore, it is thought that the miRNAs in polyphenols may contribute to the amelioration of MAFLD patients.

A study reported that the miRNA-122 and miRNA-33 levels in hepatic cells decreased following 5 hours of a 25 mg/L grape proanthocyanin treatment in mouse hepatoma cell lines.[42] Ellagitannin doses of 3.125 µg/mL, 6.25 µg/mL, 12.5 µg/mL, 25 µg/mL, and 50 µg/mL for 72 hours in human HepG2 cells demonstrated an antiproliferative effect; hsa-let-7e, hsa-miR-370, hsa-mir-373, and hsa -miR-526b were upregulated, whereas hsa-let-7a, hsa-let-7c, and hsa-let-7d were downregulated, depending on the dose and time.[43] In another study, HepG2 cells were treated with 50 mg/L of pure epigallocatechin gallate isolated from green tea (EGCG), 100 mg/L of grape seed proanthocyanin extract (GSPE) or 100 mg/L of cocoa proanthocyanidin extract (CPE). After 5 hours of treatment, miRNA-30b was downregulated by all 3 treatments, and EGCG or CPE treatments upregulated the level of miRNA-1224-3p, miRNA-197, and miRNA-532-3p.[15] In another study, the administration of 0.1 µg/mL, 0.2 µg/mL, 2 µg/mL, and 20 µg/mL of EGCG to HepG2 cells revealed that miRNA-221, miRNA-181a, and miRNA-10b were upregulated in a dose-dependent manner, indicating that EGCG inhibited osteopontin-dependent injury and fibrosis. [44]

It has been established that obesity and dyslipidemia negatively affect the development of MAFLD.[4] Studies have shown that the treatment of preadipocyte cells with polyphenols improved miRNA levels. For example, administration of 25 µM of trans-resveratrol, trans-resveratrol-3-O-sulfate, trans-resveratrol-3'-O-glucuronide (3G) or trans-resveratrol-4'-O-glucuronide (4G) treatment in 3T3-L1 to maturing pre-adipocytes during differentiation for 8 days resulted in 3G and 4G inhibition in adipogenesis through upregulation of miRNA-155.[45] Other research confirmed that miRNA-17-5p was upregulated in 3T3-L1 matured pre-adipocyte cells following 25 µM curcumin treatment. Additionally, miRNA-17-5p was found to target levels of the tcf7L2 gene, reducing the risk of diabetes, and had an inhibiting effect on adipogenesis. [46] Human pre-adipocyte cells treated with 25 µmol/L of extra-virgin olive oil polyphenols for 6 hours resulted in upregulation of intracellular let-7c levels and downregulation in miRNA-155 and miRNA-34a levels, which were inversely correlated with the degree of inflammation. Accordingly, the levels of miRNA-155-5p, miRNA-34a-5p, and let-7c-5p, associated with the nuclear factor kappa β (NF-κB) pathway, were inversely modulated by tumor necrosis factor alpha (TNF-α) in both cells and exosomes. It was suggested that these interactions could have a significant effect on reducing obesity-related inflammation.[47]

ii. *In Vivo* Studies

The development of MAFLD is characterized by a degenerative antioxidant balance and progressive inflammation, and the accumulation of fatty acids in the liver. MAFLD increases with obesity, which is often associated with comorbid metabolic diseases. The prevalence of MAFLD is approximately 65% in obese patients and may be as high as 85% in the morbidly obese.[48] To our knowledge, there have been no *in vivo* studies that have investigated the relationship between polyphenols and miRNAs in MAFLD.We examined the relationship between polyphenols and miRNAs in obese mice or rat models fed with a high-fat diet due to the significant correlation between obesity and MAFLD.

A study demonstrated that miRNA-122 and miRNA-125b in female mice were upregulated with 2 mg/g quercetin treatment for 6 weeks compared with 0.2 mg/g quercetin treatment.[49] In other research, mice were fed a control diet, a high-fat diet, or a high-fat diet treated with 0.5% to 1.0% coffee polyphenols (CPP) for 2-15 weeks and increased miRNA-122 levels were seen. Additionally, the mRNA level of sterol regulatory element-binding protein (SREBP)-1c, acetyl-CoA carboxylase-1 and -2, stearoyl-CoA desaturase-1, and pyruvate dehydrogenase kinase-4 in the liver were significantly lower in mice fed with CPP.[50] In another study, mice were fed a control or a high-fat diet and treated with a high dose of quercetin for 10 weeks. The flavonoid treatment resulted in regulated expression of miRNA-103, miRNA-107, and miRNA-122. The study suggested that polyphenols may be able to prevent or weaken the metabolic effects of a high-fat and high-cholesterol diet when administered in a continuous dose, indicating the importance of dietary intervention in the treatment of MAFLD.[51]

In other research, rats were fed a lard oil diet or lard oil with 250 mg/kg of GSPE for 3 weeks and downregulation of miRNA-122 and miRNA-33 was observed. These results suggested that proanthocyanidin treatment increased hepatic cholesterol efflux to produce new high-density lipoprotein (HDL) particles by inhibiting miRNA-33, and decreased lipogenesis by inhibiting miRNA-122.[42] Another study reported that 500 mg/kg of green tea treatment for 12 weeks led to upregulation of miRNA-335 in adipose tissue in mice fed a high-fat diet. Consequently, miRNA-335 downregulated genes involved in insulin signaling and lipid metabolism. On the other hand, green tea inhibited TNF-α levels.[52] In addition, the upregulation of miR-221 was observed after 16 weeks with green tea treatment (20 mg/kg) treatment in rats with thioacetamide (TAA)-induced hepatic fibrosis. Treatment with EGCG blocked the effects of TAA and inhibited osteopontin-dependent injury and fibrosis.[44] According to another study, upregulated miRNA-17-5p inhibited adipogenesis and decreased diabetes risk by suppressing the Wnt signal pathway effector Tcf7l2 gene in mice fed a high-fat diet or high-fat diet with curcumin (2 µM dose for 6 days and 10 µM on day 7).[46]

It has also been observed that treatment with 30 mg/kg of resveratrol for 8 weeks resulted in decreased fatty acid synthase and SREBP1 protein levels and increased carnitine palmitoyltransferase-1a levels in obese rats. Fatty acid synthase was reduced after miRNA-122-5p transfection; miRNA-122-5p transfection; carnitine palmitoyl transferase-1a was downregulated by the over-expression of miRNA-107-3p. The study showed that SREBF1 is a target gene for miRNA-103-3p and miRNA-107-3p, FASN is a target for miRNA-122-5p, and CPT1A is a target for miRNA-107-3p.[53] It has also been noted that in mice or apoE$^{-/-}$ mice fed with 0.006% quercetin, hesperidin, naringenin, anthocyanin, catechin, curcumin, proanthocyanin, caffeic acid, or ferulic acid or a control diet, mmu-miRNA-291b-5p and mmu-miRNA-296-5p were upregulated, while mmu-miRNA-30c-1, mmu-miRNA-467b and mmu-miRNA-374 were downregulated after 8 weeks.[54] The effects of polyphenols on miRNAs as reported in various studies are provided in Table 3.

Discussion

The precise prevalence of MAFLD is not known, but it is increasing rapidly alongside diseases such as diabetes, dyslipidemia, and particularly obesity. The prevalence among obese individuals has been estimated at 65%, and it can be as much as 85% in the morbidly obese.[48] Today, obesity is a pandemic; worldwide, more than 1.9 billion adults are overweight and 600 billion adults are obese.[55] Obesity plays a key role in the development of MAFLD, as well as genetic predisposition and environmental factors, such as dietary habits.[56] Several invasive and

noninvasive methods are used in the diagnosis of MAFLD. Although a biopsy, an invasive method, is the current gold standard, it has many disadvantages due to the potential for serious complications, such as severe pain, bleeding, infection, and even death, and it can therefore be difficult to apply in the clinic.[57,58] Noninvasive methods, such as liver enzyme tests, ultrasound, and other imaging methods are widely used, but these are not sufficient to define the stage and subtype of MAFLD.[57] There is a growing need to identify new and reliable biomarkers.

miRNAs are stable and can be detected in plasma, serum, and other biological fluids.[19] Several studies have shown that miRNAs may represent a useful tool to diagnose the stage and the subtype of MAFLD.[8,20-35] Research has demonstrated that the serum level of miRNA-122 is particularly high in MAFLD patients.[6,21-25,28,35,59] Additionally, miRNA-34a is upregulated in patients with NASH and can serve as a reliable biomarker to distinguish between MAFLD and NASH.[20,21,27-29] The miRNA pathways thought to have a relationship in the diagnosis and prognosis of MAFLD are shown in Table 2, but further studies are needed to confirm the pathways and whether miRNAs can be used accurately in the diagnosis of MAFLD.

As yet, there is no pharmacological treatment for MAFLD; only lifestyle modification with diet therapy and physical activity is recommended.[60] Fruits and vegetables are the basis of a healthy diet, and are also rich in polyphenols.[37] A link has been established that polyphenols positively affect health through action to alter gene expression encoding essential metabolic proteins. These gene modifications may be the result of the interaction of polyphenols with epigenetic factors, such as signal cascades and/or miRNAs,[18] but the exact mechanisms are still unknown.[9,14] It has been demonstrated that polyphenols can contribute to improving MAFLD, but, to our knowledge, no study has yet shown the relationship between polyphenols and miRNAs in MAFLD. Studies of obese, high-fat diet-fed mice and rats, and *in vitro* studies linked to liver and pre-adipocyte cell lines have shown that polyphenols can modulate the miRNA profiles in liver disease, particularly MAFLD, but the studies and polyphenol groups examined are limited.[13,41-53] Moreover, there has been no clinical study to date. *In vitro*, *in vivo*, and clinical studies are urgently needed to further demonstrate and explain the relationship between polyphenols and miRNAs for MAFLD patients.

Conclusion

It is fairly certain that miRNAs can have a role in the diagnosis and prognosis of MAFLD and could provide an easy and practical noninvasive method for the diagnosis of MAFLD. Polyphenols have been shown to contribute to the amelioration of MAFLD, as in many diseases, and may modulate miRNAs in MAFLD due to their antioxidant, anti-inflammatory, antidiabetic, anticancer properties, as well as improve lipid metabolism, it is not yet possible to determine the exact effects of polyphenols on miRNAs in MAFLD. Future studies may be a source of hope for diet therapy recommendations for MAFLD patients and the development of polyphenol-related foods or drugs that target miRNAs.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – HMB, FE, FEG; Design – HMB, FE, FEG; Supervision – HMB, FE, FEG; Literature review – HMB; Writing – HMB; Critical review – FE, FEG.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Eslam M, Sanyal AJ, George J. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020;158(7):1999-2014. [CrossRef]
2. Kawano Y, Cohen DE. Mechanisms of hepatic triglyceride accumulation in non-alcoholic fatty liver disease. J Gastroenterol 2013;48(49):434–441.
3. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol 2020;73(1)202-209. [CrossRef]
4. Cohen JC, Horton JD, Hobbs HH. Human fatty liver disease: Old questions and new insights. Science 2011;332(6037):1519-1523. [CrossRef]
5. Gerhard GS, DiStefano JK. Micro RNAs in the development of non-alcoholic fatty liver disease. World J Hepatol 2015;7(2):226-234. [CrossRef]
6. Pirola CJ, Gianotti TF, Castaño GO, Mallardi P, Martino JS, Ledesma MMG, et al. Circulating microRNA signature in non-alcoholic fatty liver disease: From serum non-coding RNAs to liver histology and disease pathogenesis. Gut 2015;64(5):800-812. [CrossRef]
7. Esquela-Kerscher A, Slack FJ. Oncomirs - MicroRNAs with a role in cancer. Nat Rev Cancer 2006;6(4):259-269. [CrossRef]
8. Rome S. Use of miRNAs in biofluids as biomarkers in dietary and lifestyle intervention studies. Genes Nutr 2015;10(5):483. [CrossRef]
9. Milenkovic D, Jude B, Morand C. miRNA as molecular target of polyphenols underlying their biological effects. Free Radic Biol Med 2013;64:40-51. [CrossRef]
10. Septembre-Malaterre A, Le Sage F, Hatia S, Catan A, Janci L, Gonthier MP. Curcuma longa polyphenols improve insulin-mediated lipid accumulation and attenuate proinflammatory response of 3T3-L1 adipose cells during oxidative stress through regulation of key adipokines and antioxidant enzymes. BioFactors 2016;42(4):418-430. [CrossRef]
11. Rodriguez A, Vauzour D, Krueger CG, Shanmuganayagam D, Reed J, Calani L, et al. Bioavailability, bioactivity and impact on health of dietary flavonoids and related compounds: an update. Arch Toxicol 2014;88(10):1803-1853. [CrossRef]
12. Mazidi M, Kengne AP. Higher adherence to plant-based diets are associated with lower likelihood of fatty liver. Clin Nutr 2019;38(4):1672-1677. [CrossRef]
13. Salomone F, Ivancovsky-Wajcman D, Fliss-Isakov N, Webb M, Grosso G, Godos J, et al. Higher phenolic acid intake independently associates with lower prevalence of insulin resistance and non-alcoholic fatty liver disease. JHEP Rep 2020;2(2):100069. [CrossRef]
14. Corrêa TAF, Rogero MM. Polyphenols regulating microRNAs and inflammation biomarkers in obesity. Nutrition 2019;59:150-157. [CrossRef]
15. Arola-Arnal A, Bladé C. Proanthocyanidins Modulate MicroRNA Expression in Human HepG2 Cells. PLoS One 2011;6(10):e25982. [CrossRef]
16. Ceccarelli S, Panera N, Gnani D, Nobili V. Dual role of microRNAs in NAFLD. Int J Mol Sci 2013;14(4):8437-8455. [CrossRef]
17. Lakner AM, Bonkovsky HL, Schrum LW. microRNAs: Fad or future of liver disease. World J Gastroenterol 2011;17(20):2536-2542. [CrossRef]
18. Bladé C, Baselga-Escudero L, Salvadó MJ, Arola-Arnal A. miRNAs, polyphenols, and chronic disease. Mol Nutr Food Res 2013;57(1):58-70. [CrossRef]
19. Weber JA, Baxter DH, Zhang S, Huang DY, Huang KH, Lee MJ, et al. The microRNA spectrum in 12 body fluids. Clin Chem 2010;56(11):1733-1741.
20. Soronen J, Yki-Järvinen H, Zhou Y, Sädevirta S, Sarin AP, Leivonen M, et al. Novel hepatic microRNAs upregulated in human nonalcoholic fatty liver disease. Physiol Rep 2016;4(1):e12661. [CrossRef]
21. Cermelli S, Ruggieri A, Marrero JA, Ioannou GN, Beretta L. Circulating microRNAs in patients with chronic hepatitis C and non-alcoholic fatty liver disease. PLoS One 2011;6(8):e23937. [CrossRef]
22. Yamada H, Suzuki K, Ichino N, Ando Y, Sawada A, Osakabe K, et al. Associations between circulating microRNAs (miR-21, miR-34a, miR-122 and miR-451) and non-alcoholic fatty liver. Clin Chim Acta 2013;424:99-103. [CrossRef]

23. Tan Y, Ge G, Pan T, Wen D, Gan J. A pilot study of serum micrornas panel as potential biomarkers for diagnosis of nonalcoholic fatty liver disease. PLoS One 2014;9(8):e105192. [CrossRef]
24. Celikbilek M, Baskol M, Taheri S, Deniz K, Dogan S, Zararsiz G, et al. Circulating microRNAs in patients with non-alcoholic fatty liver disease. World J Hepatol 2014;6(8):613-620. [CrossRef]
25. Miyaaki H, Ichikawa T, Kamo Y, Taura N, Honda T, Shibata H, et al. Significance of serum and hepatic microRNA-122 levels in patients with non-alcoholic fatty liver disease. Liver Int 2014;34(7):e302-e307. [CrossRef]
26. Becker PP, Rau M, Schmitt J, Malsch C, Hammer C, Bantel H, et al. Performance of serum microRNAs-122,-192 and-21 as biomarkers in patients with non-Alcoholic steatohepatitis. PLoS One 2015;10(11):e0142661. [CrossRef]
27. Sun C, Huang F, Liu X, Xiao X, Yang M, Hu G, et al. miR-21 regulates triglyceride and cholesterol metabolism in non-alcoholic fatty liver disease by targeting HMGCR. Int J Mol Med 2015;35(3):847-853. [CrossRef]
28. Liu XL, Pan Q, Zhang RN, Shen F, Yan SY, Sun C, et al. Disease-specific miR-34a as diagnostic marker of nonalcoholic steatohepatitis in a Chinese population. World J Gastroenterol 2016;22(44):9844-9852. [CrossRef]
29. Zarrinpar A, Gupta S, Maurya MR, Subramaniam S, Loomba R. Serum microRNAs explain discordance of non-alcoholic fatty liver disease in monozygotic and dizygotic twins: a prospective study. Physiol Behav 2016;65(9):1546-1554. [CrossRef]
30. Salvoza NC, Klinzing DC, Gopez-Cervantes J, Baclig MO. Association of circulating serum MIR-34a and MIR-122 with dyslipidemia among patients with non-alcoholic fatty liver disease. PLoS One 2016;11(4):e0153497. [CrossRef]
31. Akuta N, Kawamura Y, Suzuki F, Saitoh S, Arase Y, Kunimoto H, et al. Impact of circulating miR-122 for histological features and hepatocellular carcinoma of nonalcoholic fatty liver disease in Japan. Hepatol Int 2016;10(4):647-656. [CrossRef]
32. Auguet T, Aragonès G, Berlanga A, Guiu-Jurado E, Martí A, Martínez S, et al. miR33a/miR33b* and miR122 as Possible Contributors to Hepatic Lipid Metabolism in Obese Women with Nonalcoholic Fatty Liver Disease. Int J Mol Sci 2016;17(10):1620. [CrossRef]
33. Guo Y, Xiong Y, Sheng Q, Zhao S, Wattacheril J, Flynn CR. A microRNA expression signature for human NAFLD progression. J Gastroenterol 2016;51(10):1022-1030. [CrossRef]
34. Latorre J, Moreno-Navarrete JM, Mercader JM, Sabater M, Rovira Ò, Gironès J, et al. Decreased lipid metabolism but increased FA biosynthesis are coupled with changes in liver microRNAs in obese subjects with NAFLD. Int J Obes 2017;41(4):620-630. [CrossRef]
35. López-Riera M, Conde I, Tolosa L, Zaragoza Á, Castell JV, Gómez-Lechón MJ, et al. New microRNA biomarkers for drug-induced steatosis and their potential to predict the contribution of drugs to non-alcoholic fatty liver disease. Front Pharmacol 2017;8:3. [CrossRef]
36. López-Riera M, Conde I, Quintas G, Pedrola L, Zaragoza A, Perez-Rojas J, et al. Non-invasive prediction of NAFLD severity: a comprehensive, independent validation of previously postulated serum microRNA biomarkers. Sci Rep 2018;8:10606. [CrossRef]
37. Szczepaniak OM, Kobus-Cisowska J, Kusek W, Przeor M. Functional properties of Cornelian cherry (Cornus mas L.): a comprehensive review. Eur Food Res Technol 2019;245:2071-2087. [CrossRef]
38. Bayram HM, Ozturkcan SA. Bioactive components and biological properties of cornelian cherry (Cornus mas L.): A comprehensive review. J Funct Food 2020;75:104252. [CrossRef]
39. Sengul IY, Yucel E. Antimicrobial properties of wild fruits. Biol Divers Conserv 2015;8(1):69-77.
40. Bladé C, Baselga-Escudero L, Arola-Arnal A. microRNAs as new targets of dietary polyphenols. Curr Pharm Biotechnol 2014;15(4):343-351. [CrossRef]
41. Rodriguez-Ramiro I, Vauzour D, Minihane AM. Polyphenols and non-alcoholic fatty liver disease: Impact and mechanisms. Proc Nutr Soc 2016;75(1):47-60. [CrossRef]
42. Baselga-Escudero L, Bladé C, Ribas-Latre A, Casanova E, Salvadó MJ, Arola L, et al. Grape seed proanthocyanidins repress the hepatic lipid regulators miR-33 and miR-122 in rats. Mol Nutr Food Res 2012;56(11):1636-1646. [CrossRef]
43. Wen XY, Wu SY, Li ZQ, Liu ZQ, Zhang JJ, Wang GF, et al. Ellagitannin (BJA3121), an anti-proliferative natural polyphenol compound, can regulate the expression of MiRNAs in HepG2 cancer cells. Phyther Res 2009;23(6):778-784. [CrossRef]
44. Arffa ML, Zapf MA, Kothari AN, Chang V, Gupta GN, Ding X, et al. Epigallocatechin-3-gallate upregulates miR-221 to inhibit osteopontin-dependent hepatic fibrosis. PLoS One 2016;11(12):e0167435. [CrossRef]
45. Eseberri I, Lasa A, Miranda J, Gracia A, Portillo MP. Potential miRNA involvement in the anti-adipogenic effect of resveratrol and its metabolites. PLoS One 2017;12(9):e0184875. [CrossRef]
46. Tian L, Song Z, Shoa W, Du WW, Zhao LR, Zeng K, et al. Curcumin represses mouse 3T3-L1 cell adipogenic differentiation via inhibiting miR-17-5p and stimulating the Wnt signalling pathway effector Tcf7l2. Cell Death Dis 2017;8(1):e2559. [CrossRef]
47. Carpi S, Scoditti E, Massaro M, Polini B, Manera C, Digiacomo M, et al. The extra-virgin olive oil polyphenols oleocanthal and oleacein counteract inflammation-related gene and mirna expression in adipocytes by attenuating NF- κB activation. Nutrients 2019;11(2):2855. [CrossRef]
48. Divella R, Mazzocca A, Daniele A, Sabbà C, Paradiso A. Obesity, nonalcoholic fatty liver disease and adipocytokines network in promotion of cancer. Int J Biol Sci 2019;15(3):610-616. [CrossRef]
49. Boesch-Saadatmandi C, Wagner AE, Wolffram S, Rimbach G. Effect of quercetin on inflammatory gene expression in mice liver in vivo - Role of redox factor 1, miRNA-122 and miRNA-125b. Pharmacol Res 2012;65(5):523-530. [CrossRef]
50. Murase T, Misawa K, Minegishi Y, Aoki M, Ominami H, Suzuki Y, et al. Coffee polyphenols suppress diet-induced body fat accumulation by down-regulating SREBP-1c and related molecules in C57BL/6J mice. Am J Physiol Endocrinol Metab 2011;300(1):E122-E133. [CrossRef]
51. Joven J, Espinel E, Rull A, Aragonès G, Rodríguez-Gallego E, Camps J, et al. Plant-derived polyphenols regulate expression of miRNA paralogs miR-103/107 and miR-122 and prevent diet-induced fatty liver disease in hyperlipidemic mice. Biochim Biophys Acta 2012;1820(7):894-899. [CrossRef]
52. Otton R, Bolin AP, Ferreira LT, Marinovic MP, Rocha ALS, Mori MA. Polyphenol-rich green tea extract improves adipose tissue metabolism by down-regulating miR-335 expression and mitigating insulin resistance and inflammation. J Nutr Biochem 2018;57:170-179. [CrossRef]
53. Gracia A, Fernández-Quintela A, Miranda J, Eseberri I, González M, Portillo MP. Are miRNA-103, miRNA-107 and miRNA-122 involved in the prevention of liver steatosis induced by resveratrol? Nutrients 2017;9(4):360.
54. Milenkovic D, Deval C, Gouranton E, Landrier JF, Scalbert A, Morand C, et al. Modulation of miRNA expression by dietary polyphenols in apoE deficient mice: A new mechanism of the action of polyphenols. PLoS One 2012;7(1):e29837. [CrossRef]
55. World Health Organization. [Internet]. Obesity and overweight; 2015. Available at: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed on January 12, 2021.
56. Festi D, Schiumerini R, Marzi L, Di Biase AR, Mandolesi D, Montrone L, et al. Review article: the diagnosis of non-alcoholic fatty liver disease -- availability and accuracy of non-invasive methods. Aliment Pharmacol Ther 2013;37(4):392-400. [CrossRef]
57. Liu Z, Wang Y, Borlak J, Tong W. Mechanistically linked serum miRNAs distinguish between drug induced and fatty liver disease of different grades. Sci Rep 2016;6:23709. [CrossRef]
58. Seeff LB, Everson GT, Morgan TR, Curto TM, Lee WM, Ghany MG, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. Clin Gastroenterol Hepatol 2010;8(10):877-883.[CrossRef]

59. Akuta N, Kawamura Y, Suzuki F, Saitoh S, Arase Y, Fujiyama S, et al. Analysis of association between circulating miR-122 and histopathological features of nonalcoholic fatty liver disease in patients free of hepatocellular carcinoma. BMC Gastroenterol 2016;16(1):141.[CrossRef]
60. Glass O, Filozof C, Noureddin M, Berner-Hansen M, Schabel E, Omokaro SO, et al. Standardization of diet and exercise in clinical trials of NAFLD-NASH: recommendations from the liver forum. J Hepatol 2020;73(3):680-693. [CrossRef]
61. Su Q, Kumar V, Sud N, Mahato RI. MicroRNAs in the pathogenesis and treatment of progressive liver injury in NAFLD and liver fibrosis. Adv Drug Deliv Rev 2018;129:54-63. [CrossRef]
62. Esau C, Davis S, Murray SF, Yu XX, Pandey SK, Pear M, et al. miR-122 regulation of lipid metabolism revealed by in vivo antisense targeting. Cell Metab 2006;3(29):87-98. [CrossRef]
63. Elmén J, Lindow M, Schütz S, Lawrence M, Petri A, Obad S, et al. LNA-mediated microRNA silencing in non-human primates. Nature 2008;452(7189):896-899. [CrossRef]
64. Hsu SH, Wang B, Kota J, Yu J, Costinean S, Kutay H, et al. Essential metabolic, anti-inflammatory, and anti-tumorigenic functions of miR-122 in liver. J Clin Invest 2012;122(8):2871-2883. [CrossRef]
65. Zheng L, Lv GC, Sheng J, Yang YD. Effect of miRNA-10b in regulating cellular steatosis level by targeting PPAR-α expression, a novel mechanism for the pathogenesis of NAFLD. J Gastroenterol Hepatol 2010;25(1):156-163. [CrossRef]
66. Rayner KJ, Suárez Y, Dávalos A, Parathath S, Fitzgerald ML, Tamehiro N, et al. MiR-33 Contributes to the Regulation of Cholesterol Homeostasis. Science 2010;328(5985):1570-1573. [CrossRef]
67. Dávalos A, Goedeke L, Smibert P, Ramírez CM, Warrier NP, Andreo U, et al. miR-33a/b contribute to the regulation of fatty acid metabolism and insulin signaling. Proc Natl Acad Sci U S A 2011;108(22):9232-9237. [CrossRef]
68. Gerin I, Clerbaux LA, Haumont O, Lanthier N, Das AK, Burant CF, et al. Expression of miR-33 from an SREBP2 intron inhibits cholesterol export and fatty acid oxidation. J Biol Chem 2010;285(44):33652-33661. [CrossRef]
69. Min HK, Kapoor A, Fuchs M, Mirshahi F, Zhou H, Maher J, et al. Increased hepatic synthesis and dysregulation of cholesterol metabolism is associated with the severity of nonalcoholic fatty liver disease. Cell Metab 2012;15(5):665-674. [CrossRef]
70. Castro RE, Ferreira DM, Afonso MB, Borralho PM, Machado MV, Cortez-Pinto H, et al. MiR-34a/SIRT1/p53 is suppressed by ursodeoxycholic acid in the rat liver and activated by disease severity in human non-alcoholic fatty liver disease. J Hepatol 2013;58(1):119-125. [CrossRef]
71. Vilà L, Elias I, Roca C, Ribera A, Ferre T, Casellas A, et al. AAV8-mediated Sirt1 gene transfer to the liver prevents high carbohydrate diet-induced non-alcoholic fatty liver disease. Mol Ther-Methods Clin Dev 2014;1:4039.
72. Sacco J, Adeli K. MicroRNAs: emerging Roles in Lipid and Lipoprotein Metabolism. Curr Opin Lipidol 2012;23(3):220-225. [CrossRef]
73. Coll M, Taghdouini A, Perea L, Mannaerts I, Vila-Casadesús M, Blaya D, et al. Integrative miRNA and gene expression profiling analysis of human quiescent hepatic stellate cells. Sci Rep 2014;5:11549. [CrossRef]
74. Iizuka M, Ogawa T, Enomoto M, Motoyama H, Yoshizato K, Ikeda K, et al. Induction of microRNA-214-5p in human and rodent liver fibrosis. Fibrogenes Tissue Repair 2012;5(1):12. [CrossRef]
75. Ji J, Zhang J, Huang G, Qian J, Wang X, Mei S. Over-expressed microRNA-27a and 27b influence fat accumulation and cell proliferation during rat hepatic stellate cell activation. FEBS Lett 2009;583(4):759-766. [CrossRef]
76. Ng R, Wu H, Xiao H, Chen X, Willenbring H, Steer CJ, et al. Inhibition of microRNA-24 expression in liver prevents hepatic lipid accumulation and hyperlipidemia. Hepatology 2014;60(2):554-564. [CrossRef]
77. Hur W, Lee JH, Kim SW, Kim JH, Bae SH, Kim M, et al. Downregulation of microRNA-451 in non-alcoholic steatohepatitis inhibits fatty acid-induced proinflammatory cytokine production through the AMPK/AKT pathway. Int J Biochem Cell Biol 2015;64:265-276. [CrossRef]
78. de Conti A, Ortega JF, Tryndyak V, Dreval K, Moreno FS, Rusyn I, et al. MicroRNA deregulation in nonalcoholic steatohepatitisassociated liver carcinogenesis. Oncotarget 2017;8(51):88517-8828. [CrossRef]
79. Liu XL, Cao HX, Wang BC, Xin FZ, Zhang RN, Zhou D, et al. miR-192-5p regulates lipid synthesis in non-Alcoholic fatty liver disease through SCD-1. World J Gastroenterol 2017;23(46):8140-8151. [CrossRef]
80. Trajkovski M, Hausser J, Soutschek J, Bhat B, Akin A, Zavolan M, et al. MicroRNAs 103 and 107 regulate insulin sensitivity. Nature 2011;474(7353):649-653. [CrossRef]
81. Xu Q, Li Y, Shang YF, Wang HL, Yao MX. MiRNA-103: Molecular link between insulin resistance and nonalcoholic fatty liver disease. World J Gastroenterol 2015;21(2):511-516. [CrossRef]
82. Blaya D, Aguilar-Bravo B, Hao F, Casacuberta-Serra S, Coll M, Perea L, et al. Expression of microRNA-155 in inflammatory cells modulates liver injury. Hepatology 2018;68(2):691-706. [CrossRef]
83. Wang L, Zhang N, Wang Z, Ai D, Cao Z, Pan H. Decreased MiR-155 level in the peripheral blood of non-alcoholic fatty liver disease patients may serve as a biomarker and may influence LXR activity. Cell Physiol Biochem 2016;39(6):2239-2248. [CrossRef]
84. Ahn J, Lee H, Chung CH, Ha T. High fat diet induced downregulation of microRNA-467b increased lipoprotein lipase in hepatic steatosis. Biochem Biophys Res Commun 2011;414(4):664-669. [CrossRef]
85. Lynn FC. Meta-regulation: microRNA regulation of glucose and lipid metabolism. Trends Endocrinol Metab 2009;20(9):452-459. [CrossRef]