

Role of micrornas in the pathophysiology and diagnosis of metabolic dysfunction-associated steatotic liver disease: A bibliometric review

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) has become a public health problem, given its increasing incidence worldwide and strong association with metabolic syndrome components such as obesity, insulin resistance, and systemic inflammation. Recent studies have shown the relevance of microRNAs (miRNAs) as potential biomarkers and therapeutic targets in MASLD. This bibliometric review aimed to evaluate the scientific production of the last decade on miRNAs involved in the pathophysiology and diagnosis of MASLD. A total of 775 articles were initially retrieved from the PubMed database, with 51 meeting the inclusion criteria after a systematic screening process. Bibliometric analysis showed that China and the United States had the highest number of publications, with studies published mainly by the International Journal of Molecular Sciences and Hepatology. Among the most studied miRNAs were miR-122, miR-29a, miR-34a, and miR-223, which participate in lipid metabolism, inflammation, fibrosis, and insulin sensitivity. Co-authorship network analysis identified Gao Bin as the most influential author in the field. Keyword co-occurrence analysis showed growing interest in miRNAs in general, miR-29a, miR-34a, miR-122, miR-223, nonalcoholic fatty liver disease, lipogenesis, and mitochondrial stress in recent years. This review emphasizes the increasing scientific attention on miRNAs involved in MASLD and highlights their diagnostic and therapeutic potential. However, further studies are still needed for the identification and clinical validation of therapeutic targets that modulate miRNAs. Future perspectives include the integration of omics approaches and the exploration of nutritional or pharmacological strategies for miRNA modulation.

Keywords: Biomarkers; inflammation; microRNA; miR-122; miR-29a; miR-34a; nonalcoholic fatty liver disease; nonalcoholic steatohepatitis.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) has become a relevant public health problem with increasing incidence worldwide.^[1] Epidemiological studies indicate a prevalence of approximately 38% in the adult population and of 7% to 14% among children and adolescents (Elsaid et al., 2022).^[2] MASLD is more prevalent in Latin America (~44%) than in Western Europe (~25%), likely due to differences in lifestyle and dietary patterns.^[3,4]

Recent epidemiological studies suggest that MASLD prevalence will increase significantly by 2040, reaching approximately 55% of the world population.^[3] This growth is predicted to be particularly high among individuals belonging to risk groups, including obese patients, those with type 2 diabetes (T2DM), and individuals with insulin resistance. The association of insulin resistance, T2DM, obesity, and dyslipidemia in patients with metabolic syndrome and MASLD suggests a strong link between these two conditions, pointing to shared underlying causes.^[5,6]

MASLD progression can culminate in more severe conditions, such as nonalcoholic steatohepatitis, liver fibrosis, cirrhosis, and hepatocellular carcinoma. A lipid accumulation of less than 5% of the hepatocyte volume is considered physiological, whereas values above this threshold are indicative of MASLD.^[7] Clinical studies indicate that between 12% and 40% of individuals with MASLD progress to nonalcoholic steatohepatitis. Of these, approximately 15% to 25% progress to liver cirrhosis, and approximately 7% of patients with cirrhosis progress to hepatocellular carcinoma.^[8] These data underscore the importance of early diagnosis and continuous monitoring of MASLD, especially in at-risk populations, to prevent serious complications.^[9] In addition to hepatic complications, MASLD is associated with several extrahepatic manifestations, suggesting the presence of systemic pathogenic mechanisms. These complications include chronic kidney disease, extrahepatic neoplasms, and cardiovascular diseases, which contribute significantly to morbidity and mortality in this population.^[10,11]

Early diagnosis of MASLD is essential for the implementation of prevention and therapeutic intervention strategies. However, diagnosis is often difficult in the early stages of the disease, as conventional hepatic serological markers, such as alanine aminotransferase (ALT) and aspartate transaminase (AST), may be within reference values. Liver biopsy remains the diagnostic gold standard but is an invasive method.^[9,12] Given these limitations, recent research has focused on identifying new diagnostic and prognostic biomarkers for MASLD. Among the most promising are microRNAs (miRNAs), small non-coding RNA regulatory molecules that have been investigated for their potential value in early detection, risk stratification, and monitoring of disease progression.^[13,14]

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miRNAs exhibit numerous advantages as biomarkers and therapeutic targets, such as high stability, detectability in body fluids, and central regulatory roles in MASLD-associated metabolic, inflammatory, and fibrogenic processes. Recent studies indicated that some miRNAs, such as miR-122, miR-34a, and miR-29a, are highly expressed in individuals with MASLD, actively participating in the modulation of hepatic inflammation, insulin resistance, dyslipidemia, and hepatic fibrosis. miR-122 was associated with the degree of liver injury and metabolic disorders, whereas miR-34a was shown to participate in the regulation of lipid metabolism and hepatic fibrogenesis, acting on several molecular targets involved in disease progression.^[14–16] Another example is miR-29a, which can regulate epigenetic mechanisms, particularly through interaction with DNA methyltransferases, directly modulating hepatic inflammatory and fibrogenic processes.^[15,17] Interestingly, dietary interventions and bioactive compounds have demonstrated potential in modulating the expression of these miRNAs, offering alternative and complementary approaches for MASLD treatment and prevention.^[18]

In view of these considerations, this bibliometric review aimed to evaluate the scientific production of the last 10 years on miRNAs involved in MASLD, highlighting their possible clinical and therapeutic applications. The guiding question of the research was: What are the trends and scientific contributions on the role of miRNAs in MASLD in recent years?

Materials and Methods

This study combined a bibliometric approach and a review of the literature to understand the role of miRNAs in MASLD. First, a bibliometric review was conducted to identify research trends, collaboration networks, and the academic impact of studies addressing miRNAs in the context of MASLD in the last 10 years. Next, a synthesis of the selected studies was carried out.

Bibliometric Review

This review adopted an analytical approach and focused on articles indexed by PubMed. PubMed was chosen for its broad scope, reliability, and relevance in the biomedical field. It provides open access to a vast database, including MEDLINE, which compiles publications from peer-reviewed journals with high scientific rigor. Additionally, PubMed is continuously updated, guaranteeing access to the most recent and relevant publications in the fields of health and biological sciences, enhancing the robustness of this review.

The search strategy was designed based on the research question and the Problem–Interest–Context–Outcome (PICO) framework.^[19] The Problem (P) was the lack of noninvasive diagnostic and prognostic markers in MASLD. The Interest (I) was the use of serum miRNAs in the diagnosis, prognosis, and therapeutic management of MASLD in a health Context (C). No specific Outcomes (O) were included in the search. The search string comprised descriptors connected by Boolean operators: “miRNA” OR “microRNA” AND “nonalcoholic fatty liver disease” OR “NAFLD” OR “metabolic dysfunction-associated steatotic liver disease” OR “MASLD.”

Initially, articles were selected based on titles and abstracts. Then, a rigorous screening was performed, excluding studies that were not original articles, such as systematic reviews, narrative reviews, commentaries, errata, and studies based exclusively on bioinformatics analyses. The remaining articles were analyzed for relevance and methodological quality, resulting in the definitive inclusion of those that met the pre-established criteria. Preference was given to applied research (experimental laboratory studies or clinical studies).

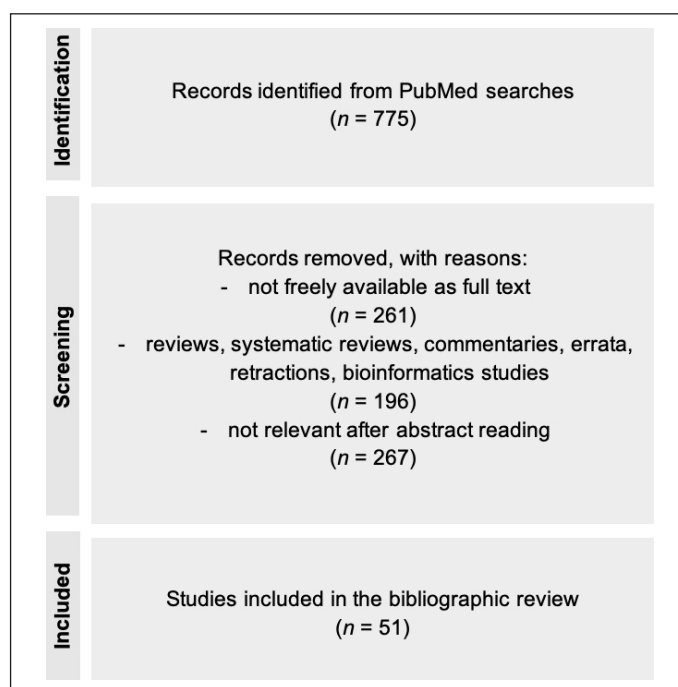


Figure 1. Flowchart detailing the steps in the bibliographic review.

The selected articles were analyzed to identify scientific collaboration networks between researchers and institutions, influential authors, emerging topics, publication patterns, frequent terms in titles and abstracts (minimum of five occurrences per term), prominent countries, and most-cited articles. These parameters were analyzed using VOSviewer® software version 1.6.19 (van Eck and Waltman, 2010).

Results and Discussion

Bibliometric Analysis

The literature search was conducted in the PubMed database, retrieving 775 articles. Of these, 261 records were removed for not being freely available in full text, and 514 articles were retained. After an initial screening, 196 articles were excluded because they were reviews, systematic reviews, commentaries, errata, retractions, or bioinformatics analyses. Of the remaining articles subjected to an in-depth screening, 51 met the eligibility criteria and were included in this review (Fig. 1). This process enabled the selection of relevant and methodologically appropriate studies to support the critical analysis of the findings, strengthening the conclusions on the topic. Appendix 1 summarizes the articles included in the review.

The synthesis of articles presented in Appendix 1 explores the role of miRNAs in the regulation of lipid metabolism, inflammation, liver fibrosis, and insulin resistance, particularly in the context of MASLD/NAFLD and associated conditions. Among the most studied miRNAs, miR-122, miR-29a, miR-34a, and miR-223 deserve mention for their therapeutic and diagnostic potential.

miR-122 is described as a key regulator of hepatic lipid metabolism, fibrosis, and inflammation. Several studies have shown that elevated serum levels of miR-122 positively correlate with the severity of hepatic steatosis, lobular inflammation, and fibrosis. As such, this miRNA is more sensitive than traditional liver enzymes, such as ALT and AST, in the noninvasive diagnosis of the disease. Modulation of miR-122, espe-

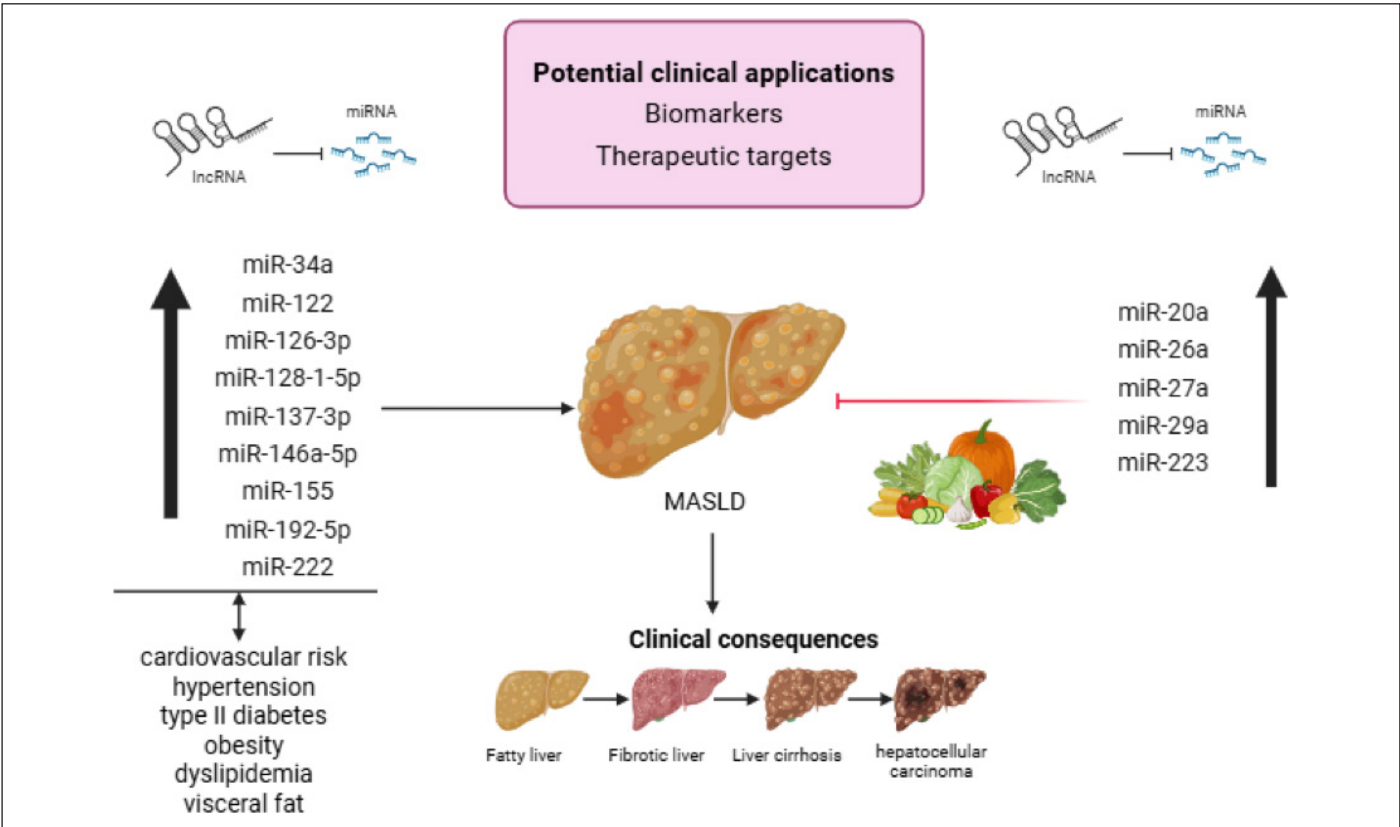


Figure 2. Role of microRNAs in the regulation of metabolic dysfunction-associated steatotic liver disease (MASLD): potential biomarkers and therapeutic targets.

cially through the LKB1/AMPK pathway and interaction with SIRT1, emerges as a promising therapeutic strategy to reduce hepatic lipid accumulation and improve metabolic homeostasis.^[20,29–31,34,37,42,45,51,52,54,61,65]

The studies addressed in this review indicated that miR-29a protects against hepatic steatosis and fibrosis through the regulation of inflammatory and fibrogenic pathways. Its hepatic expression reduces lipid accumulation and inflammation, modulating pathways such as TGF- β /SMAD3, PI3K, and those of proteins associated with the inflammatory response (e.g., IL6 and MCP1). Its protective role against mitochondrial stress is also highlighted, having the potential to reduce the development of fibrosis and hepatic inflammation induced by high-fat diets.^[15,17,22,23,27,54,67]

The results demonstrated that miR-34a is related to the worsening of MASLD, intensifying steatosis, inflammation, and hepatocyte apoptosis. Its elevated expression distinguishes MASLD from other liver diseases, presenting a superior diagnostic performance to conventional markers (CK-18, ALT, and indices such as FIB-4 and APRI). Therapeutic modulation of miR-34a could therefore represent a promising approach to controlling the progression of MASLD and its complications, including insulin resistance and associated cardiovascular disease.^[58–60]

miR-223 demonstrates significant anti-inflammatory and antifibrotic effects, often associated with intercellular communication via extracellular vesicles. Selective transfer of miR-223 from neutrophils to hepatocytes reduces inflammation and fibrosis. It is suggested as a relevant therapeutic target to halt the progression of MASLD to NASH and hepatocellular carcinoma.^[35,41,43,49]

Some studies evaluated nutritional and pharmacological interventions for miRNA modulation. The Mediterranean diet and supplementation

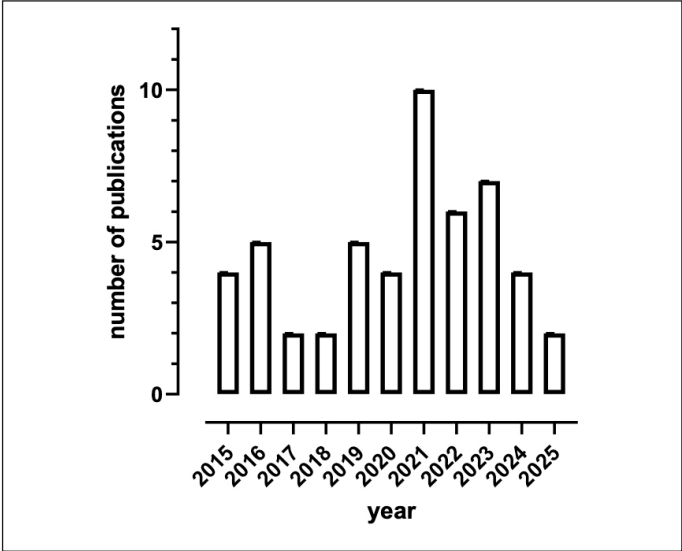


Figure 3. Temporal analysis of publications on microRNAs in the context of metabolic dysfunction-associated steatotic liver disease.

with δ -tocotrienol and resveratrol were shown to be capable of reducing the expression of inflammatory miRNAs, improving the metabolic profile in patients with metabolic syndrome. Furthermore, regular physical activity reduced pro-inflammatory miRNAs such as miR-146a-5p, highlighting the preventive potential of these approaches against metabolic and hepatic complications.^[18,58]

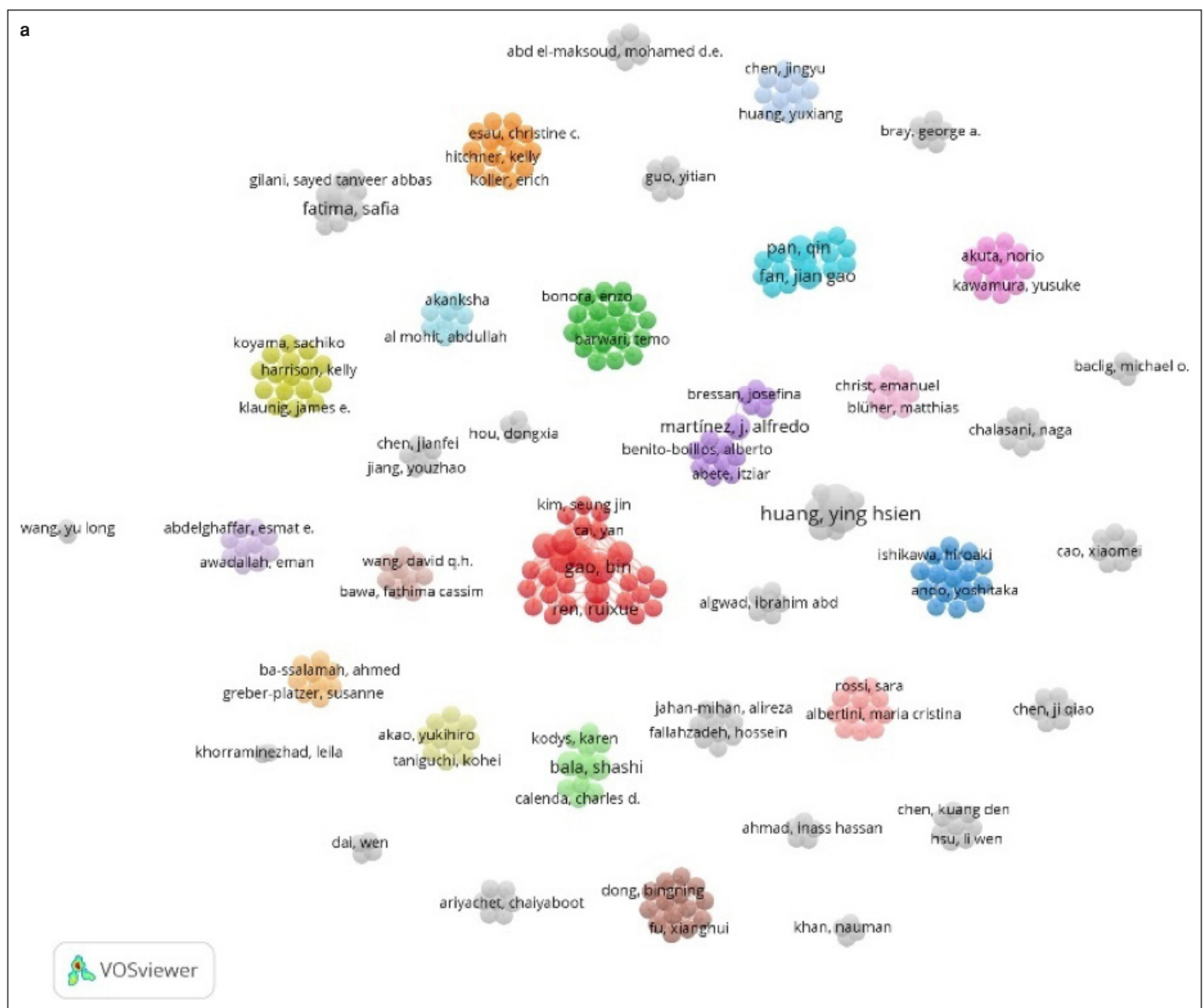


Figure 4. (a) Bibliometric network map and **(b)** overlay visualization map of the main authors of scientific publications on microRNAs in the context of metabolic dysfunction-associated steatotic liver disease. Cont →

Taken together, these findings reinforce the importance of miRNAs as central regulators of lipid metabolism, inflammation, and progression of liver fibrosis, as well as their viability as noninvasive biomarkers for the diagnosis and therapeutic monitoring of MASLD and related metabolic diseases. Interventions targeting the modulation of these miRNAs offer promising therapeutic perspectives but require further clinical validation in studies with larger populations and different metabolic contexts. A schematic summary of the results is shown in Figure 2.

Temporal Analysis of Publications

Temporal analysis of the publications included in this review revealed an increase in the number of studies from 2020 onward (Fig. 3), reflecting the growing scientific interest in miRNAs in the context of MASLD. This increase followed the rise in the global incidence of the disease, reinforcing the relevance of the topic in recent years. According to data

presented by Le et al.,^[3] by 2040, more than half of the adult population will have MASLD, with the increases being more pronounced in women, smokers, and those without metabolic syndrome. Such projections are mainly associated with lifestyle changes, genetic factors, visceral fat deposition, and high consumption of sugar and saturated fat. These factors favor systemic inflammation and insulin resistance, culminating in several associated pathological conditions, such as MASLD and cardiovascular diseases, hypertension, and metabolic syndrome.^[4]

Most studies were conducted in China, accounting for about 30% of all publications, followed by the United States, with approximately 20%. Studies were mainly published by the International Journal of Molecular Sciences (~14%) and Hepatology (~10%), reflecting the preference for journals with a high impact factor in the areas of molecular biology and hepatology. The impact factor of the main journals on the topic ranged from 5 (International Journal of Molecular Sciences) to 14 (Hepatology) and 20 (Journal of Hepatology).

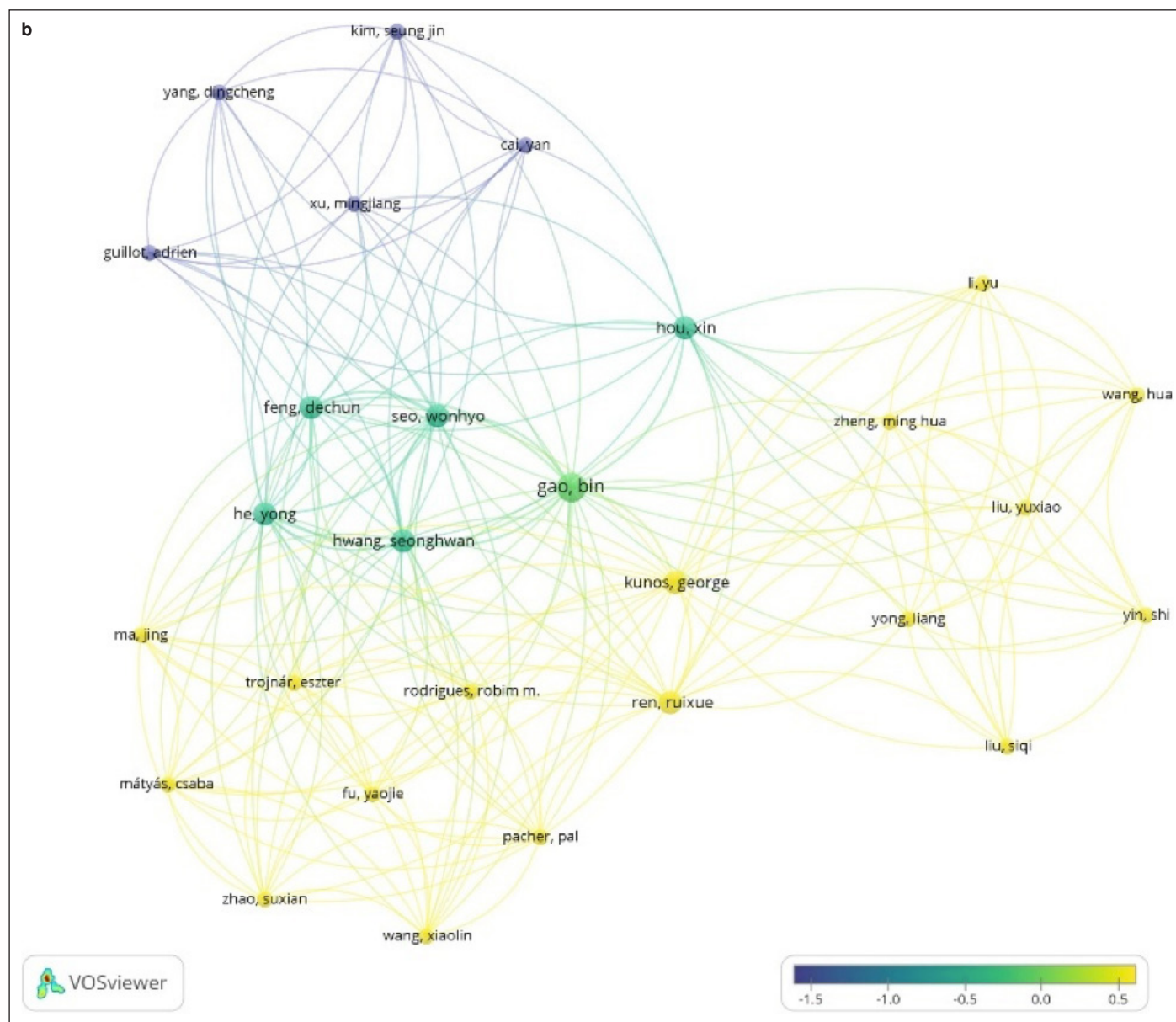


Figure 4.

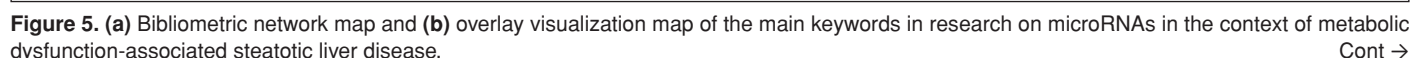
The predominance of publications from China may be associated with the growing incidence of MASLD in the country, estimated at 46 new cases per 1,000 inhabitants/year, according to recent data in the literature.^[68–70] In the United States, the high scientific production can be explained by the high prevalence of risk factors for MASLD, such as obesity, insulin resistance, and metabolic syndrome, which affect a significant portion of the adult population.^[4]

Bibliometric analysis, performed using VOSviewer software, indicated that the authors with the highest citation strength were Gao Bin, with a link strength of 34, and Bonora Enzo, with a link strength of 18. These findings underscore the influence and protagonism of these authors in scientific production related to miRNAs in the context of MASLD.

Figure 4 shows the results of the co-authorship network analysis. Several clusters (Fig. 4a) represented by different colors can be observed, indicating communities of authors who collaborate more frequently

with each other. The author Gao Bin stands out as one of the central nodes of the network, exhibiting a strong degree of connection with other authors. This finding suggests significant collaborative action and a possible leadership or reference role in the subject. Other well-defined groups include those led by Pan, Qin, Bonora, Enzo, Akuta, Norio, Koyama, and Sachiko, which reflect regional or thematic centers of scientific production. Figure 4b confirms the influence of Gao Bin, who is placed as the main central node. This high betweenness centrality is indicative of the author's strategic role in connecting different sub-groups within the network. Gao's position suggests a strong influence on the production and dissemination of knowledge on the topic.

A dense cluster of highly interconnected authors was formed around Gao, including Seo, Wonhyo, Feng, Dechun, Hwang, Seonghwan, He, Yong, Hou, and Xin. This pattern suggests the existence of a well-established collaborative core, possibly linked to the same institution



The predominant green and yellow colors in the network (Fig. 4b) indicate positive normalization values in contribution analysis, reinforcing

the active role of the authors in the generation and circulation of recent knowledge on the topic. This configuration points to a robust and integrated collaborative structure, which favors the advancement of knowledge about the role of miRNAs in the pathophysiology of MASLD and their diagnostic and therapeutic potential. Additionally, Figure 4a shows a considerable number of isolated authors, that is, those with few connections in the network (indicated in gray), suggesting independent studies with little international or interdisciplinary collaboration. This fragmentation may indicate an opportunity for strengthening collaborative networks and promoting integration between research groups.

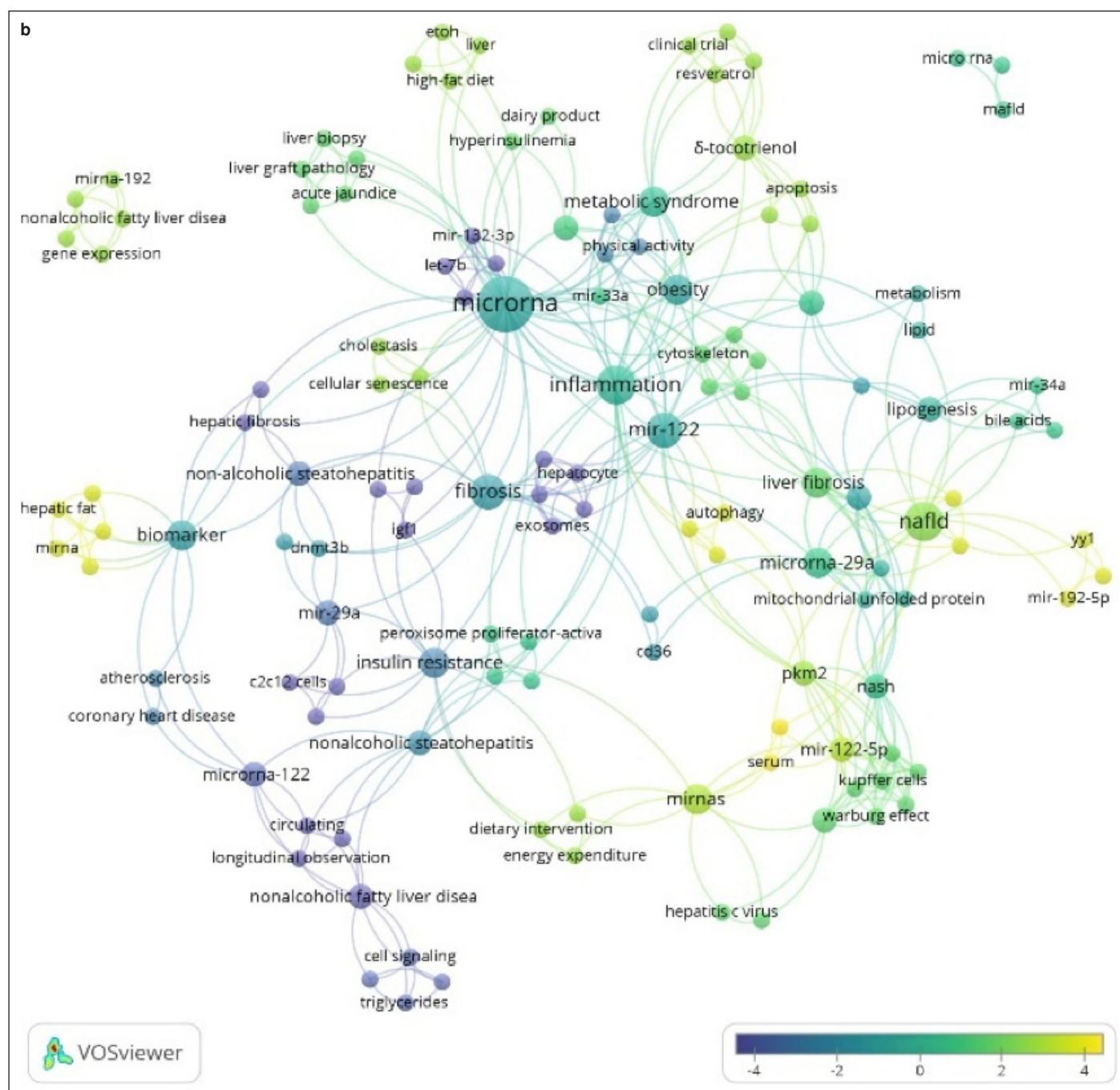


Figure 5.

The main countries of affiliation were China, the United States, and Japan. These findings reinforce the role of these nations as centers of scientific production on miRNAs and MASLD.

Keyword Analysis

Figure 5 shows the network of keyword co-occurrences extracted from the selected articles. This analysis aimed to identify the main themes, conceptual interrelations, and emerging trends in the scientific literature on miRNAs and MASLD. The cluster density map revealed multiple clusters, with the term “microRNA” appearing as a central node (Fig.

5a). This term was connected to the keywords inflammation, fibrosis, obesity, insulin resistance, NAFLD, and biomarker. Thus, studies have been exploring the role of miRNAs in inflammatory processes, hepatic fibrogenesis, and insulin resistance, which are central mechanisms in the pathophysiology of MASLD. The most recurrent miRNAs were miR-122, miR-29a, miR-34a, miR-192, miR-33a, and miR-192-5p, indicating a growing interest in their application as potential biomarkers or therapeutic targets.

The themes nonalcoholic steatohepatitis, fibrosis, autophagy, and lipogenesis have been gaining prominence, suggesting a convergence of

studies on molecular pathways that regulate both the progression and regression of liver damage. The presence of other key terms, such as clinical trial, resveratrol, and δ -tocotrienol, indicates the investigation of translational approaches and potential therapies.

Figure 5b shows the temporal overlay map of keywords. The most recent keywords appear in yellow and light green, whereas the oldest terms are displayed in blue. Terms such as miR-29a, miR-192-5p, autophagy, mitochondrial unfolded protein, Kupffer cells, serum, and NAFLD appear prominently in the most recent publications, suggesting that these themes represent current frontiers of research on miRNAs in the context of MASLD.

This analysis allowed the identification of gaps and future opportunities, particularly in the clinical validation of miRNAs as diagnostic tools and the study of their molecular mechanisms in cellular and animal models. New studies are needed to consolidate the use of miRNAs in the diagnosis, prognosis, and possibly treatment of MASLD.

Bibliometric analysis revealed a significant correlation between MASLD and metabolic syndrome, demonstrating the interrelation of MASLD with several pathological conditions, such as insulin resistance, dyslipidemia, and systemic inflammation.

It is also important to highlight the need for further investigation into the molecular mechanisms mediated by miRNAs, especially miR-122, miR-29a, and miR-223, which emerged as potential therapeutic targets. miR-122 is strongly associated with the promotion of hepatic and systemic inflammatory processes, contributing to the progression of MASLD to cirrhosis and hepatocellular carcinoma. By contrast, miR-29a and miR-223 demonstrate hepatoprotective effects, attenuating inflammation and hepatic fibrosis.

Deepening our understanding of the regulatory pathways modulated by these miRNAs is essential for elucidating the pathophysiological mechanisms of MASLD, which has increased in prevalence globally, including among children and adolescents. Furthermore, the use of these miRNAs as biomarkers may represent a promising strategy for early diagnosis. Their modulation by dietary interventions, physical activity, or specific drugs also emerges as a potentially effective therapeutic approach.

A limitation of this bibliometric review was the restricted access to the full texts of approximately one-third of the initially retrieved publications. This constraint may have resulted in the exclusion of relevant high-quality studies, potentially influencing the comprehensiveness of the analysis. Future reviews should consider strategies to improve access to full-text content, such as institutional or interlibrary collaborations, in order to ensure broader and more representative inclusion of the available literature.

Future Perspectives

This review demonstrated the relevance of miRNAs as potential biomarkers and therapeutic targets of MASLD. Despite recent advances in understanding the molecular pathways modulated mainly by miR-122 and miR-29a, important gaps remain to be explored.

Future studies should prioritize the clinical validation of these miRNAs in longitudinal and multicenter trials, aiming to consolidate their application in clinical practice for both early diagnosis and disease monitoring. Standardization of methods for collecting, extracting, and quantifying circulating miRNAs is essential for their effective use as a diagnostic tool.

Another gap in research involves investigating the therapeutic potential of modulating miRNAs through nutritional interventions, bioactive compounds, physical activity, or therapies using agomiRs or antagomiRs. The combination of pharmacological approaches with miRNA-based therapies may represent an innovative and personalized strategy for the management of MASLD and its complications. Therefore, there is a need for additional *in vivo* and *in vitro* studies, as well as *in silico* analyses, to elucidate the pathways regulated by miRNAs in MASLD.

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

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Appendix 1. Summary of articles included in the review

Reference	Objective	Main findings
Csak et al. (2015) [20]	Evaluate miR-122 regulation of HIF-1 α , vimentin, and MAP3K3 in liver fibrosis.	- $\downarrow$ liver miR-122, $\uparrow$ HIF-1 α , vimentin, and MAP3K3 expression, $\uparrow$ hepatic steatosis. - $\uparrow$ serum miR-122 in hepatic steatosis associated with diet
Fu et al. (2015) [21]	Investigate miR-26a in hepatic metabolic regulation and insulin sensitivity.	- $\uparrow$ liver miR-26a, $\uparrow$ insulin sensitivity and $\downarrow$ metabolic complications of obesity, $\downarrow$ glucose production and lipid biosynthesis.
Galimov et al. (2015) [22]	Investigate miR-29a and targets in GH-induced insulin resistance.	- GH therapy, $\uparrow$ IGF-1, $\downarrow$ miR-29a, $\downarrow$ insulin signaling, COLA3A1, and $\uparrow$ myokines, fibrosis, inflammation, and insulin resistance.
Mattis et al. (2015) [23]	Evaluate how miR-29a modulates LPL and lipid handling in steatosis.	- $\downarrow$ miR-29, $\uparrow$ liver LPL, $\uparrow$ liver triglyceride (TG) and cholesterol, metabolic dysfunction-associated steatotic liver disease.
Akuta et al. (2016) [24]	Analyze circulating miR-122 in relation to NAFLD histopathology.	- $\uparrow$ serum miR-122, $\uparrow$ steatosis progression, lobular inflammation, and fibrosis progression.
Marques-Rocha et al. (2016) [25]	Evaluate how a Mediterranean diet modulates inflammatory miRNAs in metabolic syndrome.	- Mediterranean diet consumption improved miR-155 and Let-7b expression. $\uparrow$ Let-7b, $\downarrow$ reactive oxygen species (ROS) production.
Salvoza et al. (2016) [26]	Explore associations of key serum miRNAs with dyslipidemia in NAFLD.	- Patients with NAFLD had $\uparrow$ expression of miR-34a and miR-122 compared to healthy patients. $\uparrow$ miR-34a and miR-122, $\uparrow$ degree of steatosis, fibrosis, and inflammation. Serum miR-122 was higher than ALT values in patients with NAFLD.
Zhou et al. (2016) [27]	Investigate miR-29a and insulin resistance in IUGR-exposed muscle cells.	- $\uparrow$ miR-29a induced insulin resistance in C2C12 cells. $\uparrow$ miR-29a, $\downarrow$ GLUT-4 and PPAR α .
Liu et al. (2016) [28]	Evaluate circulating miRNAs for NASH diagnosis and differentiation from CHB.	- miR-122, -16, -192, and -34a showed significant differential expression between NAFLD and CHB patients. miR-34a was significantly increased in NAFLD compared to CHB. - The levels of miR-122, miR-192, and especially miR-34a correlated positively with hepatic steatosis and inflammatory activity (lobular inflammation and hepatocyte ballooning). Only miR-16 showed significant correlation with hepatic fibrosis. - miR-34a showed superior diagnostic performance to the other markers (CK-18, ALT, FIB-4, and APRI) in identifying patients with NASH, reaching high specificity (0.875) and moderate sensitivity (0.704).
Wu et al. (2017) [29]	Investigate miR-122 in lipid accumulation and droplet regulation.	- $\uparrow$ miR-122, $\downarrow$ accumulation of lipids in hepatocytes, YY1-FXP-SHP axis modulation.
Willeit et al. (2017) [30]	Explore miR-122 as a biomarker for MetS and T2DM risk.	- $\uparrow$ miR-122, $\uparrow$ ALT, AST, adiposity, inflammation, insulin resistance, triglycerides and $\downarrow$ HDL-C.
Wang and Yu (2018) [31]	Explore the link between miR-122 and coronary atherosclerosis severity.	- $\uparrow$ circulating levels of miR-122, $\uparrow$ stage of coronary atherosclerotic lesion and $\uparrow$ cholesterol and TG.
Russo et al. (2018) [32]	Explore changes in miR-126 and miR-146a-5p after physical activity in obesity.	- Obesity is directly correlated with $\uparrow$ miR-146a-5p, $\uparrow$ miR-146a-5p, $\uparrow$ total cholesterol and TG, $\downarrow$ HDL-C. In U937 cells, $\uparrow$ miR-146a-5p $\rightarrow$ $\uparrow$ TLR4, NF κ B, IL6, and TNF α .
Yang et al. (2019) [15]	Evaluate miR-29a in reducing hepatic inflammation and fibrosis in dietary NASH.	- $\uparrow$ miR-29a, $\downarrow$ hepatic lipid accumulation, as evidenced by $\downarrow$ AST and ROS. The mechanism associated with these effects is a decrease in the expression of SMAD3, p-PI3K, LC3B II, TGF β and IL6.
Ando et al. (2019) [33]	Evaluate the association of miR-20a, 27a, and 126 with NAFLD.	- Serum levels of miR-20a and miR-27a were significantly reduced in NAFLD patients compared with normal individuals. miR-126 showed no significant difference overall but was reduced in more severe cases in men. - There was a significant association between reduced levels of miR-20a and miR-27a and NAFLD severity, even after adjustment for multiple risk factors, such as age, sex, and metabolic indicators. - miR-126 showed a weak inverse correlation with liver fibrosis index (FIB-4) but no clear correlation with disease severity.
Long et al. (2019) [34]	Evaluate miR-122 regulation of LKB1/AMPK and Sirt1 in NAFLD lipogenesis.	- <i>In vivo</i> model of NAFLD $\uparrow$ miR-122, $\downarrow$ SIRT1 - <i>In vitro</i> model of NAFLD (HepG2 and Huh7), $\downarrow$ miR-122 promoted $\uparrow$ SIRT1 via LKB1/AMPK signaling.

Appendix 1 (cont). Summary of articles included in the review

Reference	Objective	Main findings
He et al. (2019) [35]	Evaluate miR-223 regulation of inflammation and oncogenes in NASH and HCC.	- ↑ liver and serum miR-223 after 3 months of a high-fat diet to prevent the progression from simple steatosis to NASH and liver cancer. - ↓ miR-223, ↑ proliferation and HCC markers (Ki67, CxCl10, TAZ, Gpc3, Golm1), inflammatory genes (IL6), and fibrinogenic genes (COL1A1). - miR-223-knockout mice fed a high-fat diet developed liver tumors.
Lin et al. (2019) [36]	Evaluate miR-29a in HFD-induced steatohepatitis and liver fibrosis.	- ↑ miR-29a, ↓ fat accumulation and liver mass induced by a high-fat diet and improved hepatocellular steatosis and liver fibrosis, ↓ inflammation hepatic. - ↑ miR-29a, ↓ PPAR, TFAM, MCP1, IL6, alleviation of oxidative damage and obesity reduction.
Chai et al. (2020) [37]	Evaluate how a RORA agonist modulates miR-122 and NASH severity.	- Administration of RS-2982, which binds and activates the RORA transcription factor in the liver, - ↑ miR-122 in the liver and blood, - ↓ TG in the liver and muscle tissues, ↓ inflammation and fibrosis in the liver - ↑ whole-body energy expenditure, fat oxidation, and insulin sensitivity, and ↓ weight and inflammation in adipose tissue.
Huang et al. (2020) [38]	Evaluate miR-18a-5p and miR-22-3p as stress and MetS biomarkers.	- Patients with metabolic syndrome, - ↓ miR-18a-5p and miR-22-3p, - ↑ cortisol and IL-6. - ↓ miR-18a-5p and miR-22-3p, - ↑ risk of developing metabolic syndrome.
Liu et al. (2020) [39]	Evaluate hepatic exosomal miR-192-5p in NAFLD-related macrophage activation.	- Both NAFLD and NASH patients ↑ miR-192-5p - ↑ serum ALT and AST, liver iNOS, IL6, and TNF-α. - ↑ miR-192-5p - ↓ pFoxO1 but not ↓ GSK3β.
Yang et al. (2020)[17]	Evaluate miR-29a in regulating mitochondrial stress in diet-induced NASH	- ↑ miR-29a - ↓ GSK3, SIRT1, mitochondrial proteostasis stress in NASH and reducing liver fat, fibrosis progression, and inflammation.
Bala et al. (2021) [40]	Evaluate miR-155 in regulating steatohepatitis and liver fibrosis in mice.	- High-fat diet increases miR-155 - ↑ TG, Cpt1α, FABP4, FAS, ACC2, TNFα, MCP1, and vimentin, resulting in progression of fibrogenesis and worsening of NASH.
He et al. (2021) [41]	Investigate neutrophil-derived EV transfer of miR-223 and effects in NASH.	- miR-223 transfer via LDLR/APOE-dependent EVs decreased hepatic inflammation and fibrosis in NASH.
Hegazy et al. (2021) [42]	Evaluate serum levels of miR-122 as a noninvasive marker to determine the severity of MAFLD.	- Serum miR-122 increased significantly with the severity of hepatic steatosis and fibrosis, correlating with ↑ lipid profile and ↑ ALT, AST, and GGT.
Hou et al. (2021) [43]	Evaluate myeloid IL-6-driven miR-223 exosomes and their role in NAFLD fibrosis.	- IL6 stimulation in myeloid cells activates macrophages to release miR-223-enriched exosomes that migrate to hepatocytes and inhibit genes such as TAZ and Cxcl10, attenuating the progression of liver fibrosis.
Lischka et al. (2021) [44]	Evaluate miRNAs associated with inflammation in obese and metabolically affected children.	- ↑ TNFα, IL-1Ra, and procalcitonin, correlated with ↑ miRNA-122 and -192 - ↑ miRNA-122, ↑ HOMA-IR.
Refeat et al. (2021) [45]	Evaluate correlation of miR-33a/miR-122 with lipid metabolism in MetS.	- Obese and diabetic patients showed increased serum levels of miR-122 and reduced levels of miR-33a - ↑ body mass index, Wc, Wt, total cholesterol, and TG.
Xu et al. (2021) [46]	Evaluate the role of hepatocyte miR-34a in the progression of NAFLD to NASH.	- Overexpression of miR-34a exacerbated NAFLD, whereas its deletion attenuated inflammation, apoptosis, and steatosis.
Yu et al. (2021) [47]	Evaluate the effect of miR-137-3p on NAFLD through activation of the AMPK α pathway.	- miR-137-3p significantly improved NAFLD through direct activation of the AMPK α pathway, reducing oxidative stress and hepatic inflammation.

Appendix 1 (cont). Summary of articles included in the review

Reference	Objective	Main findings
Zeinali et al. (2021) [48]	Evaluate miR-122, 126-3p, and 146a as inflammatory markers in prediabetes and T2DM.	- ↑ miR-122, pre-diabetic and T2DM - ↓ miR-126-3p → pre-diabetic and T2DM - ↓ miR-146a → pre-diabetic and T2DM - miR-122 potential target → interleukin 1 receptor type 1, NFκB, PRKAB1 - miR-126-3p → insulin receptor substrate 1, SPRED1, TRAF6, IL6 - miR-146a → TNFα, IL6 - ↑ miR-122 → ↑ HOMA-IR - ↑ miR-126-3p and miR-146a → ↓ HOMA-IR.
Zhang et al. (2021) [16]	Explore PPARγ-driven regulation of hepatic stress in NASH via miR-21-5p/SFRP5.	- PPARγ, ↓ miR-21-5p/SFRP5 pathway, ↓ oxidative stress and inflammation in NASH.
Ariyachet et al. (2022) [49]	Investigate miR-223's role in hepatic stellate activation and antifibrotic potential in organoids.	- ↑ miR-223, ↓ COL1A1, COL3A1, LOXL2, and ACTA2 - miR-223 suppressed hepatic stellate cell activation and reduced fibrosis.
Elghoroury et al. (2022) [50]	Explore exosomal expression of miR-18a/222 as diagnostic markers in liver disease.	- ↑ miR-18a and ↑ miR-222 ↑ ALT, AST, bilirubin, AFP, urea, and creatinine levels.
Hu et al. (2022) [51]	Assess the role of miR-122-5p in the development of NAFLD.	- ↑ miR-122-5p → correlated with the pathogenesis of NAFLD - ↓ miR-122-5p → ↑ SOD, GSH-Px, and ↓ MDA - ↓ miR-122-5p → ↓ total cholesterol, TG, liver weight, body weight, IL6, TNFα, and IL-8. - ↓ miR-122-5p → ↑ FOXO3
Inomata et al. (2022) [52]	Evaluate miR-122-5p's role in PKM2-mediated glycolysis in NASH Kupffer cells.	- ↓ miR-122-5p activated PKM2-mediated glycolysis in Kupffer cells, contributing to inflammation and worsening of NASH. miR-122-5p and PKM2 are promising therapeutic targets for controlling hepatic inflammation and NASH progression.
Khorraminezhad and Rudkowska (2022) [53]	Evaluate miRNA modulation by dairy products and its association with glycemic profile in hyperinsulinemia.	- High dairy intake modified the expression of miRNAs (miR-106-5p and miR-122-5p), affecting glycemic profile and insulin resistance.
Lin et al. (2022) [54]	Identify hepatic miRNA expression patterns in different etiologies of acute jaundice after liver transplantation.	- Acute cholangitis → ↓ miR-122, miR-301, and miR-21 - Acute rejection → ↑ miR-122 and ↓ miR-133a - Recurrent hepatitis → ↑ miR-122, miR-301, and miR-21 - Fatty change → ↑ 133a.
Fatima et al. (2023) [18]	Determine the effects of δ-tocotrienol and resveratrol on miRNAs in MetS patients.	- Supplementation increased miR-130b and miR-221 and decreased miR-122, improving components of metabolic syndrome.
Heianza et al. (2023) [55]	Evaluate miR-128-1-5p as a marker of insulin sensitivity and energy metabolism in obesity.	- ↑ miR-128-1-5p, ↑ HOMA-IR, waist circumference, and total body fat mass.
Liang et al. (2023) [56]	Analyze miR-29a modulation in liver under prolonged HFD and ethanol exposure	- Hepatic miR-29a expression initially increased with a high-fat and high-ethanol diet, subsequently decreasing with advancing liver fibrosis.
Mollet et al. (2023) [57]	Investigate which miR-193b-3p-related metabolic pathway interferes with NAFLD/MAFLD.	- ↑ miR-193b-3p, ↓ PPARGC1A, ↑ fat droplets in the liver, ↓ expression of MTTP, ↑ TRIB1, and ↑ LDLR.
Pervez et al. (2023) [58]	Explore miRNA expression changes in NAFLD with δ-tocotrienol and α-tocopherol therapy.	- δ-Tocotrienol and α-tocopherol significantly reduced the expression of miRNAs related to steatosis, inflammation, and apoptosis (miR-122, miR-21, miR-103a-2, miR-421, miR-375, and miR-34a).
Ragab et al. (2023) [59]	Evaluate the potential of miR-34a and miR-192 as early diagnostic markers of NAFLD.	- A positive correlation was observed between miR-34a and hypertension in patients with NAFLD and plasma lipid levels and a negative correlation with the hematological markers hemoglobin and leukocytes. miR-192 showed no correlation with these markers. miR-34a was elevated in early stages of liver fibrosis and reduced in advanced stages, whereas miR-192 showed a progressive increase according to fibrosis stage.

Appendix 1 (cont). Summary of articles included in the review

Reference	Objective	Main findings
Wan et al. (2023) [60]	Evaluate the role of liver-specific microRNA-34a in ductular reaction and hepatic fibrosis during experimental cholestasis.	- In murine models with liver-specific deletion of miR-34a, there was a significant reduction in ductular reaction, cellular senescence, and liver fibrosis induced by bile duct ligation. The reduction in miR-34a was accompanied by increased expression of Sirtuin-1 (Sirt1), suggesting that Sirt1 regulation may mediate the protective effects observed in the absence of miR-34a.
Hossain et al. (2024) [61]	Determine the role of miR-122 in the regulation of inflammatory and autophagic proteins mediated by PKM2 in NAFLD.	- Reduction of miR-122 increased PKM2 and liver inflammation and reduced autophagy, exacerbating NAFLD.
Ma et al. (2024) [62]	Evaluate miR-192-5p regulation of lipid metabolism through YY1 in NAFLD.	- ↑ miR-192-5p significantly reduced liver triglyceride accumulation by inhibiting factor YY1.
Tobaruela-Resola et al. (2024) [63]	Evaluate miR-122-5p, 151a-3p, 126-5p, and 21-5p for MASLD prediction.	- miR-122-5p, miR-151a-3p, miR-126-5p, and miR-21-5p significantly correlated with steatosis, liver stiffness, and liver fat content in MASLD.
Yang et al. (2024) [64]	Investigate miR-29a's role in reducing mitochondrial stress via MAVS in diet-induced NAFLD.	- miR-29a attenuated hepatic mitochondrial stress, reducing fibrosis, steatosis, and inflammation through inhibition of the MAVS pathway in a Western diet-induced NAFLD model.
Zhang et al. (2025) [65]	Analyze differential miRNA profiles in children with NAFLD and CVD risk.	- miR-122-5p showed increased expression in patients with NAFLD, significantly correlating with cardiovascular risk and metabolic alterations.
Michalak et al. (2025) [66]	Evaluate links between miRNAs and blood/serological fibrosis indicators in NAFLD.	- ↑ miR-126-3p, ↑ miR-1-3p, and ↓ miR-197-3p, correlation with hematological indices.